Approaches for In Silico Validation of Safety (Toxicity) Data for Cosmetics

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Abstract

It has been proven that computational approaches can be used to find endpoints that can help with a cosmetic safety assessment. Thousands of mice, guinea pigs, rats, and rabbits die each year due to torturous experiments. This paradigm shift has enabled the highest number of regulations of chemical safety assessments while also mandating the use of alternate methodologies, such as in silico approaches, whenever applicable, to evaluate different products for individual users from the US and Europe and other countries worldwide. Some people believe that animal testing is a reliable and quick approach to ensure that items are safe for human consumption as it helps to find the movement of the compound through the biological membrane and its action through it. There is also a practical realization well within the toxicity testing discipline that alternative techniques would not supersede in vivo models on a resembling scale. SEURAT-I was indeed a flagship project creating the academic and developing foundations necessary to develop strategies to supplement conventional repeated

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dose systemic toxicity testing consumer monitoring with QSAR methods, read across frameworks, TTC approach, or other omics or other computational techniques. Alternative methods of testing and validating the toxicity of cosmetic products to animals must be incorporated into cosmetic industries to promote business ethics.

Keywords

Safety · Computational approaches · Cosmetics · Bio-toxicity

11.1 Introduction

The increased influences the demand and popularity of cosmetics worldwide in skin-related disparities and the need for people to look good. Globally, the cosmetic industry is enormous, reaching a value of US$ 357.5 billion in the year 2021, with an expected value to reach US$ 508.3 billion by the year 2027 (Business Wire 2022). Skin and personal care product goods, hair products, antiperspirants, scents, and cosmetics and beauty products are among some of the product kinds with segments of the market. The functional compounds are combinations of synthetic chemical compounds with overall health benefits.

When associated with consumers, the primary benchmark is safety and toxicity-free products. Thus, product testing becomes prime for any manufacturer, ensuring the quality and safety of each ingredient used, and the cosmetic product is the manufacturer's or distributor's legal responsibility. Toxicological studies also become a part of testing for the manufacturer (US-FDA 2022). A product formulator plays a crucial role in the cosmetic industry in identifying the right ingredients for the perfect blend in any personal care product. A consultant must carry out routine screening tests. It is also essential to analyze and evaluate the stability and the toxicity of the cosmetics/personal care product formulations prior to consumer use, as these come in direct contact with our skin for a significant period (Tanner 2022). Animals have been used in research to evaluate the suitability of cosmetic industry for humans.

Countless mice, small rodents, rodents, and rabbits are slaughtered annually as a consequence of such cruel investigations (Villalobos et al. 2014). In many cases, they are not given any anesthetic at all. Tests for skin and eye irritation, allergies, poisoning, and other ailments might be conducted, damage to the genome, birth abnormalities, and cancer consequences, to name a few (Rise for Animals 2022). However, animal testing is a contentious issue in both the pharmaceutical and cosmetic industries. Some people believe that animal testing is a reliable and quick approach to ensure that items are safe for human consumption.

In contrast, others argue that it is unnecessary because other testing methods are available (White 2022). According to research, customers are interested in sustainability (Sheehan and Lee 2014). Accordingly, animal testing in the cosmetics industry has always been a polarizing topic. It is crucial in the development and

safety of cosmetics while also infringing on experimental animals' survival rights. Hence, animal experimentation is immoral in cosmetology R&D and manufacturing that is because the outcomes do not really aid population well-being and the approach results in animal suffering and killings (Kabene and Baadel 2019). However, several alternatives are available, and use of such animals to test cosmetics is extremely limited.

Alternatives to animals must be incorporated into cosmetic industries to promote business ethics. Companies can use scientific barrier evaluation to discover alternatives to animal test subjects and learn how to use animals correctly in medical and cosmetics tests. A few approaches that can anticipate acts of animal remorselessness by beauty care product organizations incorporate advanced consideration of human cells or tissues, computer modeling strategies, and tests on willing volunteers. Companies must join animal-free tests to diminish the hazard of creature enduring and, as a result, progress their trade morals (Doke and Dhawale 2015). A series of toxicity tests determine a cosmetic ingredient's hazardous potential and is part of the hazard identification process. Toxicological data relevant to humans has traditionally been collected by studying the toxicological profiles of chemicals on animals, preferably utilizing the same exposure route as in people. Toxicological studies are frequently conducted via the oral route, with extrapolation to the cutaneous route required (Vinardell and Mitjans 2017). The employment of an array of computational algorithms to assess toxicity based on the chemical structure of the substances is a crucial aspect of the strategy for developing alternatives to detect the hazard of cosmetic ingredients (and several other types of chemicals). Computational techniques can include a reliable inventory of structures, toxicological information, and data databases to produce safe exposure limits, models, and algorithms. Relevant assays considering toxicity pathways, examined in high-throughput screening assays, may eventually be added to these.

The development of animal-free toxicity testing methodologies, also known as alternative tests, has become a hot topic in toxicological science, resulting in a paradigm change in traditional animal-based toxicity evaluations (Garthoff 2005; Turley et al. 2019; Gironde et al. 2020). Cosmetics made through animal research, including cosmetic materials or products, were banned by the European Union in 2013 (European Commission 2009). As a result, new methods for ensuring the protection of cosmetic products other than animal research became inevitable. As little more than an outcome, the novel toxicity analysis technologies turned its attention to a mechanism-based technique, with the intent of deeper grasp into the pathways that lead to unfavorable biochemical processes in order to better safeguard human health and the environment (Hatherell et al. 2020; Fischer et al. 2020).

Among some of the approaches for an altruistic testing alternative for laboratory safety-level evaluation are (1) in vitro methods, (2) in silico methods, (3) read-across framework, and (4) in chemical techniques (Madden et al. 2020b; Bassan et al. 2021). The techniques can be used to measure risk and internal exposure. Computational methods cover many techniques and concepts and a wide range of endpoints. It has been proven that computational approaches can be used to find endpoints that can help with a cosmetic safety assessment. This chapter aims to overview several

dry laboratory techniques for safety evaluation. The assessment of potential danger to a list of ingredients in a product is likely to be the first stage in the safety review of a cosmetic product. There are a variety of resources and approaches that can be utilized to evaluate cosmetic product ingredients.

11.2 Estimating Ingredients of Cosmetic Products: Models and Regulations

A plethora of beliefs is often made concerning exposure to ingredients of cosmetics. Scientific committee on consumes safety (SCCS) gives standardized value to the exposure of ingredients of cosmetic products frequency of product application, quantity of product applied, retentiveness, and the different ways of uptake of the product; it can be via oral administration, inhalation, or by dermal route (SCCS 2016, 2018; Madden et al. 2020b). The SCCS provides solutions for dealing with various product sensitivities while taking into account various administration approaches. The Creme RIFM model (https://www.cremeglobal.com/creme-rifm/) is another technique that covers use data from over 36,000 users from the US and European populations. This model allows you to generate the value of aggregate exposure in order to evaluate scents in compounds. It has been updated and expanded since its first release to incorporate additional cosmetics, hygiene products, and hair care (Bernauer et al. 2021; Safford et al. 2017). If the data become accessible, this method might be used to a wider spectrum of cosmetics components. The technique of probabilistic aggregate exposure modeling has been devised for fragrances and vitamins, which are arising from cosmetic product usage, nutrition, and nutraceuticals (Safford et al. 2015; Comiskey et al. 2017).

In silico models like RIFM databases are also helpful in evaluating the frequency of product utilization combination of different products used simultaneously during a day. This will evaluate different products for individual users from the USA and Europe (Tozer et al. 2019). Further data are also available on human exposure from Human Biomonitoring studies. In our day-to-day life, people are using so many unknown chemicals, remaining unaware of the effects of those chemicals—human biomonitoring tool's objective is to measure the exposure of toxic substances to people by evaluating metabolites of human samples such as blood or urine. Human biomonitoring can only integrate toxicity-level assessment information until the initial stage, but it provides valuable data for future use.

11.2.1 The Cosmetics Regulation of the European Union (EU) (EC/1223/2009)

In 2003, the EU finally agreed to ban all sorts of animal testing in its historical Seventh Amendment to the Cosmetic Directive (Directive 76/768/EEC) from September 11, 2004 (European Commission 2004, 2009, 2018). The European Commission (EC) also made sure that after that date, the commercialization (i.e.,

products import and selling) in the market that had been tested on animals outside of Europe was to be outlawed (Taylor and Rego Alvarez 2020; European Commission 2009, 2010); however, an extension for the total prohibition on the marketing of such products was allowed until March 11, 2013 (EC). In 2009, the Cosmetic Directive was rewritten as a regulation, although all of these rules remained (Regulation 1223/2009) (EC (European Commission) 2009). Cosmetics Regulation (EC) No. 1223/2009, CLP Regulation (EC No. 1272/2008), and REACH Regulation (EC No. 1907/2006) pertain to all cosmetic commodities in the EU.

In 2005, the European Partnership for Alternative Approaches to Animal Testing (EPAA) was made in coopetition venture uniting the EC, European industry trade groups, and commercial organizations to encourage the formulation and deployment of substitute regulatory evaluation methods (European Commission 2001, 2018). In 2009, the EC and Cosmetics Europe each invested 25 million Euros in the establishment of replacements for animals for long-term toxicological analysis in a program entitled SEURAT-1, in response to the imminent 2013 deadline (see www.seurat-1.eu) (Taylor and Rego Alvarez 2020); the details of this project are discussed in the later section of this chapter.

11.2.2 Organisation for Economic Cooperation and Development (OECD)

The Organisation for Economic Cooperation and Development (OECD) (www.oecd.org) is a global membership organization composed of EU and non-EU nations. One of its responsibilities is to assist participating countries in establishing and standardizing ways to evaluate the risk to public health and the environment, such as environmental exposure assessment procedures. Existing safety evaluations have focused on experiments conducted following the Test Guidelines (TG) of the OECD, which provides a degree of confidence in the returns generated. Currently, TG for in silico methods is none but needs to adapt to substitute animal experimentation with non-test approaches (Taylor and Rego Alvarez 2020); however, the OECD and numerous government entities have created a variety of publications, especially relevant to (Q) SARs, that provide guidelines about using and presenting in silico techniques. The OECD is receiving cooperation from national policymakers and researchers from North America, Europe, and Asia to popularize these tools.

11.3 Next-Generation Risk Assessment (NGRA)

The term "Next Generation Risk Assessment" (NGRA) refers to a hypothesis-driven, a risk assessment technique based on contact that incorporates *in silico*, in vitro, and *in chemico* strategies to aid in animal-free ethical decision-making (Dent et al. 2018, 2021; Rogiers et al. 2020), with a perception to incorporate additional data types within safety selection. A fundamental was published by the US National Academies of Sciences (NAS) in the year 2007 with the title "*Toxicity*

Testing in the 21st Century, A Vision and a Strategy" (NAS 2007; Krewski et al. 2010a, b; National Research Council 2007) followed by a report titled "*Exposure Science in the 21st Century* in the year 2012 (NAS 2012) and an interpretive structure of the former transcripts in the year 2017 namely '*21st Century Science to Improve Risk-Related Evaluations'"* (NAS 2017). With an emphasis on exposure concerns, this report explores the achievements and risk assessment issues are associated with analyzing and combining various forms (and quantities) of data. Instead of relying on a safety assessment of documented diseases in animals, this study asserts that concentrations that trigger modifications in cellular signaling pathways that contribute to detrimental consequences should be understood. This paper presented a desirable and possible vision, given recent developments in molecular methods, bioinformatics, and systems biology (Rogiers et al. 2020; USEPA 2014). In Europe, a unique European Chemicals Agency (ECHA) Topical Scientific Workshop on the use of data and information from new approach methodologies (NAMs) was organized in April 2016, outlining their potential and present constraints to enhance regulatory compliance and choices relating to the evaluation of chemical compounds (ECHA 2012a, b). In the year 2017, the ECHA also published a "Read Across Assessment Framework (RAAF)" to inculcate the application of read-across data in non-animal testing models (Patlewicz et al. 2018; Kuseva et al. 2019).

The International Cooperation on Cosmetics Regulation (ICCR) established nine principles for the NGRA of cosmetic ingredients in 2018, offering a viable path forward for animal-free safety decision-making. The ICCR is an international network of cosmetics regulatory bodies from Brazil, Canada, the EU, Japan, and the United States that works voluntarily. The ICCR was established in 2007 to create a transnational framework for maintaining and enabling the most significant degree of global consumer protection by fostering regulatory convergence and lowering trade barriers (Dent et al. 2018). Pace with the rapid expansion of toxicity hazard identification and risk evaluation science and the potential even by NAMs as detailed in the NAS and ECHA studies, ICCR realized a pivotal shift in the cosmetics safety review is achievable. As a response, the ICCR convened a partnership steering committee consisting of specialists from every regulating body and an industry to concur on and emphasize the essentials for incorporating NAMs into an integrated approach for assessment process of cosmetic constituents (or "Next Generation" Risk Assessment).

There are nine principles corresponding to the risk assessment's ultimate aim, how it should be carried out, and how it can be published (Fig. 11.1) (Amaral et al. 2018; Dent et al. 2018). In July 2019, a workshop was conducted to review how well the nine ICCR principles are now being actively implemented in NGRA clinical studies being undertaken in various organizations and to investigate how the approach used may enhance safety results in vulnerability assessment utilizing NAMs. The goals and accomplishments of the workshop are described in the publication by Dent et al. 2021, which are as follows:

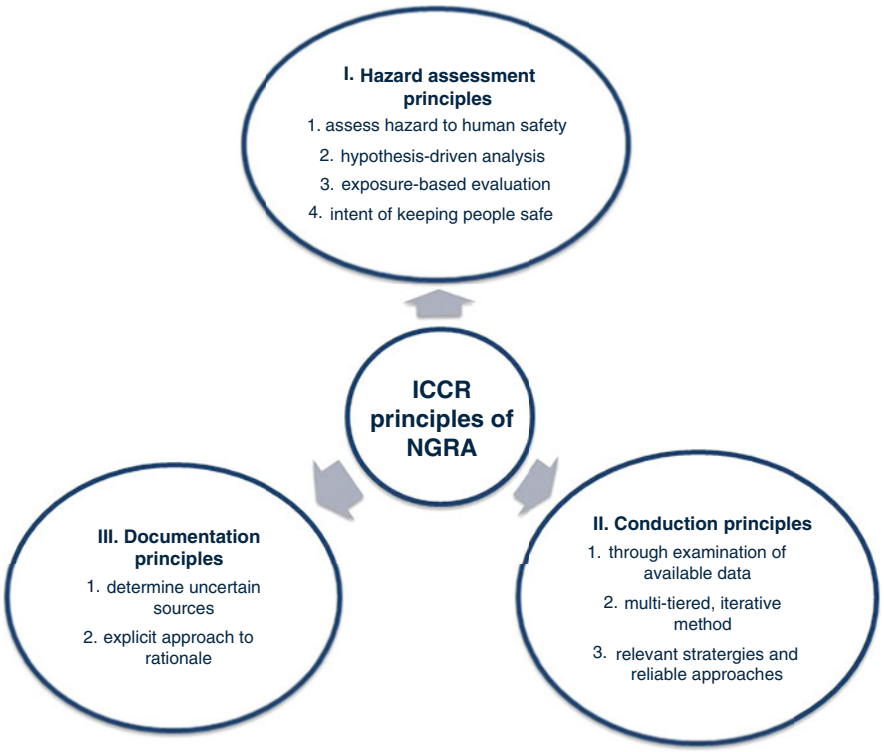

Fig. 11.1 Nine ICCR principles of NGRA that govern the adoption of new approaches in the risk analysis of cosmetic chemicals were discussed by Dent et al. (2018)

- To see whether the NGRA for cosmetic compounds can safeguard human well-being as conventional (animal-based) safety testing.
- Review some NGRA cases for cosmetic components, agree on what worked effectively, and highlight discrepancies.
- To agree on the subsequent actions that must be taken to make NGRA a regular occurrence for the hazard analysis of cosmetic compounds.

11.3.1 The Reach Chemicals Regulation (EC/1907/2006)

REACH seeks to promote human health and environmental protection by identifying chemical compounds' essential characteristics more accurately and earlier (REACH 2012). The ECHA is in charge of implementing REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) in the EU. The amendment of EU chemical legislation in 2006 facilitated the emergence of alternative approaches (European Commission 2006; Taylor and Rego Alvarez 2020), and REACH went into effect on June 1, 2007, replacing a vast number of European Directives and

Regulations with a unified framework REACH 2022). This covers the highest number of regulations of chemical safety assessments while also mandating the use of alternate methodologies, such as in silico approaches, whenever applicable. Applicants routinely recommend non-testing alternatives to ECHA to satisfy data needs for REACH. It stipulates that new in vivo data development should always be the last recourse (ECHA 2016a, b, c, 2017a, b). REACH covers all chemical substances, not just those employed in industrial processes, but also those found in our daily life, such as cleaning goods, paints, cosmetics, and articles like clothing and electrical appliances (ECHA 2012a, b; Van Der Wielen 2007). Under the REACH law, the majority of cosmetic products are classified as chemical formulations (mixtures), and each chemical substance or ingredient must be priorly indexed with the ECHA located in Helsinki if its annual quantity exceeds 1 tons (REACH Annex XII. "Standard Information Requirements for Substances Manufactured or Imported in Quantities of One Tonne or More") (Merenyi 2018), while the non-EU businesses can designate a REACH-only representative to submit pre-registrations and/or registrations (CIRS 2013) and fully comply with this regulation.

REACH only affects the cosmetics industry in part: While the steps of registration and evaluation are pertaining to cosmetic products, the stages of permission and limitations are unlikely to apply because cosmetic ingredients are regulated by numerous agencies and directives (Pouillot et al. 2009). For more information about REACH legislation, please go to http://www.cirs-reach.com/EU_REACH/REACH_Registration.html.

11.3.2 SEURAT-I Project

"Safety Evaluation Ultimately Replacing Animal Testing (SEURAT)"-I (http://www.seurat-1.eu) was a flagship project with the collaboration of 70 European public-private research joint projects (equally sponsored and funded) led by the EC's Framework Programme 7 Health Programme (https://ec.europa.eu/research/fp7/) administered by DG Research and Innovation and Cosmetics Europe (https://www.cosmeticseurope.eu/) to eliminate animal testing of chemical compounds and ensure the highest degree of consumer safety (Gocht et al. 2015; Berggren et al. 2017). The report *Toxicity Testing in the Twenty-First Century: A Vision and a Strategy* by the National Research Council of the United States (National Research Council 2007) was a massive inspiration for the program. SEURAT-I was one of the most extraordinary EU ventures on radical solutions yet undertaken. A scientific strategy was implemented around the driving premise of using a toxicological mode-of-action approach to defining how any chemical could harm public health (Boobis et al. 2008; Ankley et al. 2010; Krewski et al. 2010a, b; Gocht et al. 2015) and applies it to the development of complementing conceptual, computational (in silico), and laboratory (in vitro) model allows for the identification of numerical transit points, which is required for safety evaluations (Sturla et al. 2014). The actual objective was to make ab initio conclusions based on comprehensive knowledge of

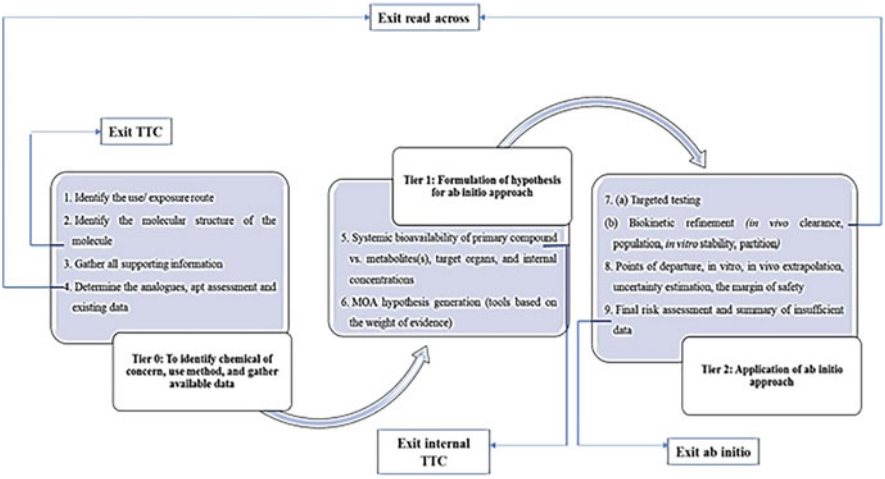

Fig. 11.2 Process flow of evaluating the efficacy of cosmetic compounds rather than using animal models for NGRA as adopted from Berggren et al. (2017) and Dent et al. (2018). (Copyright from Elsevier, first published by Berggren et al. in Computational Toxicology, 4, 2017)

toxicology pathways (Boobis et al. 2008) and to provide a standardized risk management plan approach for recurring exposure toxicity to forecast a no adverse effect level (NOAEL) of a cosmetic-relevant chemical under a given exposure circumstance (Daston et al. 2014; Thomas et al. 2013). The primary pipeline for chemical risk evaluation is built on the SEURAT-1 theoretical model but expanded, intending to provide a tool to help the evaluator through the many steps to be considered and decision-making (Berggren et al. 2017; Yang et al. 2017). We can use Thresholds of Toxicological Concern (TTC) or read-across techniques with this procedure (Schultz et al. 2015; Williams et al. 2016). SEURAT-I was indeed creating the academic and developing foundations necessary to develop strategies to supplement conventional repeated dose systemic toxicity testing consumer monitoring (Fig. 11.2).

The seven cluster projects (central data management and maintenance projects, as well as a coordination and support projects belonging to five research initiatives) under the SEURAT-I initiative include the following:

- Scr&Tox (stem cells for relevant, efficient extended and normalized toxicology)
- HeMiBio (hepatic microfluidic bioreactor)
- DETECTIVE (detection of endpoints and biomarkers of repeated dose toxicity using in vitro systems)
- COSMOS (integrated in silico models for the prediction of human repeated dose toxicity of cosmetics to optimize safety)
- Notox (predicting long-term toxic effects using computer models based on systems characterization of organotypic cultures)
- ToxBank (supporting integrated data analysis and servicing of alternative testing methods in toxicology)

- COACH ("coordination of projects on new approaches to replace current repeated dose systemic toxicity testing of cosmetics and chemicals")

11.3.2.1 The COSMOS Project

The SEURAT-1 cluster consisted of six initiatives, including COSMOS (project website address—www.cosmostox.eu). This research project was the first step toward ensuring the long-term stated goal of supplementing animal experimentation of cosmetic ingredients with safety evaluation (Cronin et al. 2012; Cronin 2015). This, in turn, alluded to the notion that further actions must be completed before the ultimate objective is accomplished. With nine countries coming together in a cluster of 15 collaborators, this project ran its term from January 1, 2011, to December 31, 2015, and had a total grant (grant agreement ID: 266835) of €6,79,733,560 and a contribution of €3,350,000 from the EU. COSMOS looked at how well the existing TTC approach could be adapted to cosmetic chemicals and then how to extend from oral to dermal route exposure, which is especially important in the case of cosmetics. The COSMOS initiative was a one-of-a-kind collaboration that addressed the cosmetic industry in terms of comprehensive screening demands without using animals (Cronin et al. 2012; Cronin 2015).

COSMOS' principal goal was to create accessible and open-source technologies and procedures for estimating the long-term detrimental consequences of cosmetic chemicals on consumers (Yang et al. 2021). The study produced implications and regulations to expand the usability and final authorities of the present TTC method for cosmetic components. On September 9, 2015, the COSMOS Symposium on Computational Tools for Safety Assessment was convened in Liverpool, United Kingdom. The one-day session provided an overview of the EU COSMOS Project's accomplishments and impact.

The International Life Sciences Institute, Europe (https://ilsi.eu/eu-projects/past-projects/cosmos/) was one of the partners of the COSMOS project and contributed as two experts groups for the TTC approach; their observations were published in the research work of Williams et al. 2016 and Yang et al. 2017. Further general information is available at the following URLs:

- COSMOS Databasehttp://www.cosmostox.eu/what/COSMOSdb/
- COSMOS Spacehttp://cosmosspace.cosmostox.eu
- COSMOS KNIME Web Portalhttp://www.cosmostox.eu/what/knime/

11.4 Intuitive and In Silico Methodologies for Impact Prediction

If there is insufficient evidence and the threshold of toxicological concern (TTC) is incapable of predicting risk, computational and in silico approaches can be used to estimate cosmetic chemicals for future hazards. There are numerous methodologies that may be used to analyze the potential serendipity of cosmetics components using in silico computational approaches. Hence, it can give information about the safety level of different ingredients in a product. Nowadays, upsurge use of computational

approaches is due to the replacement and reduction in the rate of animal testing; along with this benefit in silico approach is a cost-efficient and rapid process of toxicity assessment.

Statistical researchers use a combination of data mining algorithms to discover relationships among chemical composition and function. These models rely on data that can generate computer algorithms without the need for specialized knowledge (Tintó-Moliner and Martin 2020). A negative prediction is more accurate than a positive prediction, even though it does not rely on direct mechanistic insight. Hybrid techniques combine practical information with statistically based principles to address each flaw.

Toxicology prediction research utilizing AI has recently become popular (Wu and Wang 2018; Ciallella and Zhu 2019). Artificial intelligence (AI) is an in silico system that "adapts" the chemical composition and hazard effects of chemicals. Because animal studies are restricted, this methodology can be used to assess the safety of cosmetic compounds. AI techniques such as artificial neural networks (ANNs) and machine learning are extensively trained to determine chemical skin irritability and cytotoxicity (Hirota et al. 2015, 2018; Wilm et al. 2019).

11.4.1 Quantitative Structure–Activity Relationships (QSARs) for Dermal Absorption

QSAR is a significant technique in the field of bioinformatics. The primary goal of QSAR is to establish a statistical link between molecule characteristics and dynamics. Although machine learning techniques outperform other approaches in terms of prediction rates, they lack interpretability (Potts and Guy 1992). Most of those are professionally developed models, which, ideally, will add biochemistry, kinematic, and distal pharmacology, and suitable empirical methods toward the discussion. A cosmetic corporation will rarely engage in research unless they have a specific interest. They rely on third parties or current QSARs to construct their own to do so. Most industries, including the cosmetic industry, use QSAR to evaluate products' toxicity levels (ECHA 2016a, b, c), e.g., carcinogenicity and skin sensitization. For quantitative measurement of chemicals, first, it needs to be modeled to evaluate endpoints like ADME parameter calculation, lethal dose, and half-maximal effective concentration; second, it is required to generate descriptors based on the chemical structure of compounds to generate a model. Most of the time, interpretable descriptors are favored for the generation of QSAR. Generally used descriptors used those related to portioning tissue: blood portioning coefficient (log P). This shows the relative nature of compounds, like their hydrophobicity and lipophilicity. It helps to find the movement of the compound through the biological membrane and its action through it (Madden et al. 2020b).

At last, QSAR needs a statistical approach to link descriptor with activity (safety level or any other factor of interest (Madden et al. 2020b). Many statistic approaches were proposed, spanning from simple linear progression to multiple regression analysis, depending on whether a two or more distinct classifiers are intended. The

Potts and Guy skin permeability mathematical formulation is shown below, wherein Kp signifies the dermal coefficient of permeability.

Log Kp = 0:71 log *P*0:0061 M Wt 6:3

$N = 93$; R2 = 0.67

R2 is the "correlation coefficient" in this case, and it demonstrates the variation in Kp represented by the descriptors LogP.

The value of r describes the correlations; whether it comes out to be positive or negative correlations, a value above 0.7 for correlation coefficients shows that it is good to use. If the r-value comes close to 1, it shows very unrealistic behavior for finding biological activity (Potts and Guy 1992).

QSAR models are very approachable methods for evaluating cosmetic product ingredients for skin permeability. The data on which QSAR is based are accessible through resources such as EDETOX (https://research.ncl.ac.uk/edetox/theedetoxdatabase/) and HuskinDB (https://huskindb.drug-design.de/data/) (Hewitt et al. 2020). In a recent study, a consistent technique was used to analyze the permeability of 56 substances pertinent to cosmeceuticals across and around human skin, and it had a high degree of reproducibility (Hewitt et al. 2020). RIFM proposed another in silico approach-based model for skin absorption, primarily for epidermal rapid screening for perfumes, with a permeation value ranging between 10% and 80% premised upon Jmax (Laroche et al. 2018). Neither of these algorithms can yield definitive estimates of makeup ingredient structural accessibility following topical contact. They must be maneuvered to discern substances that have an increasing or decreasing potential for systemic bioavailability; cutaneous permeation is insufficient (Table 11.1).

11.4.1.1 Structural Rules Capturing Structure–Activity Relationships

Structural alerts are one of the simple and easy ways to assess the toxicity of compounds. Structural alerts are also known as toxic fragments. In 1985, John Ashby's concept of structural alert for structural analysis of chemical carcinogen compounds (Ashby 1985). Many structural features are responsible for the toxic properties of compounds that give rise to structural alerts like mutagenicity, skin sensitization, and organ toxicity. If any other compound shows, the same structural alert indicates the risk potential to show some effects. For example, aromatic amine and an α, β-unsaturated aldehyde are electrophiles capable of reacting with the nucleophilic site within DNA and protein, respectively, leading to skin sensitization (Madden et al. 2020b). The presence of a functional group in these compounds is responsible for eliciting toxicity or any other potential hazard (Madden et al. 2020b). The relationship between molecular structure and activity of compound can easily derive structural alert and can be used to evaluate the potential risk. Statistical analysis and interpretability are two computational approaches for finding structural alerts. Most of the methods are based on a systematic analysis approach to find some substructures that occur very frequently in toxic compounds compared to non-toxic ones. On the other side, the machine learning approach is more accepted due to algorithms for pattern detection of compounds (Cherkasov et al. 2014). SAR has also been included in a number of prognostic toxicology applications and browser

Table 11.1 A non-exhaustive collection of freely accessible professional QSAR platforms for toxicology prognosis, including carcinogenicity and genotoxicity (Kim et al. 2021)

Name of software	URL	Features
1. Ambit (IDEAconsult Ltd.)	https://ambitlri.ideaconsult.net/tool2	• For toxicity and metabolism, knowledge-based expert systems are used. AMBIT incorporates a number of in silico estimation techniques (such as Toxtree)
2. Danish QSAR predictions database (DK EPA)	http://qsar.food.dtu.dk	• Estimates primarily predicated on over 200 (Q)SARs through both public and private sources, encompassing genotoxicity and carcinogenicity throughout male and female rats and mice in vivo and in vitro
3. LAZAR (in silico toxicology, GmbH)	https://lazar.in-silico.de/predict	• Models for mutagenicity and carcinogenicity are included in this statistics-built software
4. OECD QSAR Toolbox	http://toolbox.oasis-lmc.org/	• Contains "profilers" for genotoxicity and carcinogenicity and experimental observation databases
5. Oncologic, United States Environmental Protection Agency (US EPA)	https://www.epa.gov/reviewingnewchemicals-under-toxic-substancescontrolact-tsca	• Carcinogenicity estimates based on knowledge
6. TEST (US EPA)	https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test	• Models from many external sources are included in the software, which predicts various endpoints, including Ames mutagenicity
7. Toxtree (EU JRC—IDEAconsult Ltd.)	https://eurl-ecvam.jrc.ec.europa.eu/ https://apps.ideaconsult.net/data/ui/Toxtree	• SARs are presented for cytotoxic effects, carcinogenic effects, and in vivo chromosomal aberrations test
8. VEGA (Istituto Di Ricerche Farmacologiche Mario Negri)	https://www.vegahub.eu	• In silico models and tools for assessing various endpoints, such as mutagenicity and carcinogenicity

services, as seen in Table 11.1. Toxtree is one of the user-friendly open resource software that helps find the toxic risk of compounds by using the decision tree approach. Using structural information of compounds, chemicals are kept in different toxicity classes. A toxicologist may also utilize OCHEM to anticipate the physiological characteristics of substances. The benefit of using structural alert is that results are very transparent and easily accessible, reducing testing of products on animals.

11.4.2 PBK Model

Because of ethical and legal considerations, non-animal methodologies are increasingly being conducted to estimate the sustainability of chemicals for commercial use. We show how, in the absence of additional animal evidence, a physiologically based kinetic (PBK) framework for something like the cosmetic UV blocker constituent homovalvate was constructed and validated to support its safety (Dent et al. 2021). Prior to the EU animal testing ban in 2013, the intravenous (IV) rat PBK theory was established and verified utilizing legacy in vivo data using PK-Sim® (Bessems et al. 2017). These models evaluate the parameters of chemical absorption, distribution, metabolism, and excretion (ADME) (Gellatly and Sewell 2019). The models can take into account varying modes of transmission, taxa, ages, ethnicity, sexuality, illness condition, and other characteristics. These models' purpose is to anticipate an acceptable exposure measure—a dosage parameter that is intrinsically connected to the detrimental response, such as the highest concentration, which might be attained within that tissue. The primary goal of this model seems to determine an acceptable dosage meter for assessing cytotoxic consequences. The PBK model requires appropriate knowledge for deployment in the cosmetic sector. Previously, models were created using ordinary differential equations (ODE) or MATLAB (Cronin et al. 2022). To effectively employ PBK systems, the assessment team must develop meaningful and quite well judgments concerning this same model's structure for such specific topic being discussed (e.g., which divisions are crucial and suitable exposure paradigm), as well as the legitimacy of the input parameters (exploratory or computed attributes) and the model's susceptibility toward the variables adopted (Madden et al. 2020a).

11.4.3 Grouping and Read Across

Read across is one of the conceptually simple processes for evaluating chemical safety or toxicity level. It really is the act of estimating terminal data through one or perhaps more document (origin) compounds, which are already believed for being analogous using endpoint data from one or more data-poor (target) chemicals (Berggren et al. 2015; Madden et al. 2020b). Chemicals are grouped based on shared properties they share with other groups, and information interpreted from one member of the group is used to infer from other members of the group (ECHA 2017a, b). Read across the main objective is to find similarities between the chemicals. It can be based on carbon chain length, chemical fingerprinting, mechanism of action, or specific functional groups in chemical structure (Berggren et al. 2015). ToxMatch (from IDEAconsult) and the Compound Similarity toolset (from ChemMine Tools) are two examples of software that may be used to evaluate structural similarity in compounds. Analog selection should result in an accurate read-across prognosis for in vivo responsiveness (Madden et al. 2020b). The resemblance in chemical composition, but rather more vitally, the resemblance in behavior, is factored into the equation. ADME profile (i.e., pharmacokinetics and (toxic)

Table 11.2 A list of some of the best open-source read-across utilities

Name of the tool	Features
1. AMBIT IDEAconsult Ltd. (Bulgaria) http://cefic-lri.org/lri_toolbox/ambit/	• A Web-based stand-alone tool • User-dependent qualitative approach • Manual biological similarity selection • Chemical input in the form of—name, identifiers, SMILES, InChI • Output report in the form of—s docx or xlsx, data matrix as xlsx
2. OECD Toolbox LMC, Bourgas (Bulgaria) www.qsartoolbox.org	• A stand-alone tool working on a client/server basis • Both qualitative and quantitative approaches • Presence of both manual + automatic filters for similarity search • Accepted input formats—CAS, name, SMILES, structure drawing, MOL, SDF • Output formats—IUCLID format, pdf and RTF files of prediction report, text files of data, image files of plots, etc. • Visualize data as 2D standard plots
3. CBR Fourches Lab at North Carolina State University (USA) http://www.fourcheslaboratory.com/software	• Standalone tool • Automatic biological similarity selection • Qualitative approach • Accepted formats of input are Molfile, descriptors as txt • Visualize data as a radial plot of neighbors
4. ToxRead Istituto Di Ricerche Farmacologiche Mario Negri (Italy) https://www.vegahub.eu/portfolio-item/toxread/	• Stand-alone tool • A qualitative approach to check mutagenicity while quantitative for bioconcentration factor • Automatic filters for similarity selection • Input chemical format is SMILES • Visualization of data as interactive neighbor plot • Output in the form of an image file of the plot
5. CIIPro Zhu Research Group at Rutgers University (USA) http://ciipro.rutgers.edu/	• A Web-based tool • Manual + automatic filters for similar selection • Uses the VEGA similarity algorithm • Accepted chemical formats are PubChem CID, CAS, IUPAC, SMILES, and InChI • Data visualization as activity plots

activity are toxicokinetic) (Cronin et al. 2022). Alexander-White et al., in the year 2022, based on the EU SEURAT-I project and the ICCR principles, established a pragmatic and systemic 10-step framework to illustrate how read across can be employed NAM in the absence of TTC will aid in consumer safety evaluation (Alexander-White et al. 2022) (Table 11.2).

11.4.4 The Threshold of Toxicological Concern (TTC) Approach

TTC is a statistical likelihood technique toward assessing chemical toxicity in the lack of chemical-based toxicology studies. This implies establishing a universal absolute threshold for all substances under whom there is minimal substantial risk

to individual well-being. In chemical-specific toxicity evidence, SCCS considers the TTC approach a suitable supporting tool for evaluating the safety of cosmetic compounds with known chemical structures (European Commission 2018; Worth et al. 2012; Williams et al. 2016; Yang et al. 2017). TTC values are applied using a decision framework that checks the composition of ingredients step by step. TTC's underlying database has been critical in determining robust and accurate thresholds, which requires in-depth analysis and assessment of acceptable toxicological data (Cronin et al. 2022). One of the greatest applications of the TTC approach was the basis of the EU COSMOS project (Yang et al. 2017) as it is a plausible solution to many safety risk management difficulties (Ellison et al. 2019); and it is also a part of the ab initio approach of NGRA (Daston et al. 2014; Gocht et al. 2015) as explained in the former sections of this chapter. Topical sensitivity evaluation is critical in the TTC method for cosmetic chemicals. Internal contact with cosmetic chemicals should be used in risk assessments, including the TTC approach (Kim et al. 2021). The Munro database and COSMOS dataset have been created using NOAELs (Munro et al. 1996) of chemicals obtained by oral exposure with a 100% permeability hypothesis. Williams et al. elucidated that the application of risk evaluation criteria premised on repeated dosage data of cosmetology constituents is the application of TTC (Williams et al. 2016).

11.5 The Relevance of In Silico Technologies in Adverse Outcome Pathways (AOPs)

During the last decade, the use of AOPs has indeed been established as a mechanistic utilitarian technique with vast applications in the disciplines of toxicology and mitigation strategies of chemical compounds, and their usage in the cosmetics sector is publicly recognized and highly documented as well (National Research Council 2007; Tollefsen et al. 2014; Burden et al. 2015; Vinken et al. 2020). The AOP notion indicates a robust structure that allows insights from in silico models, bioinformatics, in vitro experiments, high-throughput screening, *omics* technologies, and biological systems to be deeply implemented and unanswered questions addressed (Madden et al. 2020b). Recently, the OECD has extensively encouraged the establishment of AOPs (OECD 2012a, b; Yamada et al. 2020); the OECD-AOP initiative (www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm) is actively building a variety of AOPs for a myriad of sophisticated toxicological outcomes (OECD 2012a, b; Madden et al. 2020b; Yamada et al. 2020) after the complete ban of animal testing as inflicted by the European ordinance (EC (European Commission) 2009). The goal of AOPs is to describe and collect current understanding of the biologically viable and experimentally validated grounds for forecasting basal toxicity from mechanical evidence (OECD 2013). The AOP Knowledge Base (AOP-KB; https://aopkb.org) (Sachana 2018; Wittwehr et al. 2015), associated with its wiki (https://aopwiki.org/), and its documentation is arranged in a structured, navigable, and direct way, following a set of criteria and

guidelines (OECD 2016a, b) that make it easier to assess eligibility for specific governance needs (Wittwehr et al. 2016).

The OECD organized a workshop on "*Using Mechanistic Information in Forming Chemical Categories"* in December 2010 in Washington, DC, USA, in lieu of the situation of the *Use of Adverse Outcome Pathways in the Development of Categories* (OECD 2011a, b; Sakuratani et al. 2018). The AOP for skin sensitization was created in 2011 and 2012 (OECD 2011a, b; Schultz et al. 2016) as a reflection of the workshop's accomplishment and at the request of OECD member nations (Sakuratani et al. 2018; Schultz et al. 2016). An AOP depicts current insights into the interactions among two reference points, the molecular initiating event (MIE) (Burden et al. 2015; Ankley et al. 2010) and an adverse outcome (AO), interlinked by a sequence of key events (KEs), and whenever feasible the relations between the KEs (KERs) (Schultz et al. 2016; Delrue et al. 2016; OECD 2013).

High-throughput in vitro techniques can be used to signal hazardous potential since AOPs represent the sequence of essential processes that lead to adversity at multiple levels of biological organization (Villeneuve et al. 2014; Villeneuve 2015; Vinken et al. 2020). There is also a practical realization well within the toxicity testing discipline that alternative techniques would not supersede in vivo models on a resembling scale. Hence, AOPs will indeed be utilized to feed and lead a multidisciplinary approach (Wittwehr et al. 2016) to verification and validation; AOPs might thus serve as a link between non-animal methodologies (Burden et al. 2015; Knapen et al. 2018) and systems toxicology, thereby improving the domain of non-animal safety evaluation (Schultz et al. 2016). To assist their implementation in regulatory decision-making, there is a need for an empirical foundation to understand the outcomes of innovative test techniques and related prediction models (Tollefsen et al. 2014; Sakuratani et al. 2018). A paradigm of this type might have three key components: the AOP, non-animal test techniques, and in silico methodologies addressing essential parts of the AOP, as well as their related modeling techniques for an appropriate policy framework (Delrue et al. 2016; Yamada et al. 2020; Hecker and LaLone 2019; Wittwehr et al. 2016; Villeneuve 2015). A tangible solution to such proactive diagnostics, hypothesis-driven Integrated Approaches to Testing and Assessment (IATA), has been advocated (Tollefsen et al. 2014; OECD 2017a, b; Madden et al. 2020b).

11.5.1 The Way Forward

Blending incredibly challenging biological systems with large-scale methodologies provides a greater understanding of the complexities of the biological response to cosmetic compounds, improving the possibility of predicting clinical reactions in vivo and finding novel substitutes for animal experimentations (Zimbardi 2018). In this regard, the *omics* technology has emerged as sophisticated technology enabling trying to analyze whole genetic or molecular, or metabolite fingerprints (Lee et al. 2020a, b; Pirih and Kunej 2017), integrating analyses to enhance the evaluation and monitor the toxicity testing of cosmetic compounds (Lee et al.

2020a, b; He and Jia 2021), and offering valuable means of assessing the hazard and efficacy tests that cannot be evaluated on animals (Kim et al. 2021; van Delft et al. 2014). Cosmetics and the personal care industry are also broadening their horizons by investigating the potential of deep learning artificial intelligence (AI) and machine learning (ML) to aid in toxicity testing and product selection (Nambiar 2021; Kim and Lee 2021) for artificially creating algorithms that automatically extract facts and figures from multivariate data and analyze it even further (SciForce 2019). To generate state-of-the-art models through numerous ways, such as logistic regression, linear support vector machine (SVM), artificial neural networks (ANNs), and decision tree classifiers (Umer et al. 2020; Ma et al. 2021). Even successful businesses like that Coty and L'Oréal appear to be going into AI (de Jesus 2020) through virtual mirrors and Alexa skills, which might suggest how AI will inevitably change the panorama of the cosmetics and personal care sector over the next couple of years (Ma et al. 2021).

11.6 Conclusions

Animal cruelty has always been the dispute concerning animal experimentation and the need for searching for alternative testing methods. It has indeed been a constant conflict, but at the very minimum, a stagnation that researchers and scientists need to take a strong stance and make their moral judgments. In vitro and in silico approaches are gaining momentum as technology develops and shifts the battle-ground slightly. Various computational techniques are available for assessing safety levels, estimating exposure, and hazard identification for any cosmetic products. The organizational dimension has lately managed to include a repercussion: Several controlled trials are simply too expensive, take too long, or generate inaccurate results (Meigs 2018). High advances are that lots of high-quality databases are available for toxicology evaluation. They provide well-curated information, which reduces the use of animals in research to evaluate the safety-level assessment of cosmetic products. Recent advances in technology and understanding of mechanistic approaches, primarily through AOP, have helped prove a more insightful side of computational and in silico approaches for predicting the toxicity level of a product. Computational techniques range from structural rules to various databases and models read-across approaches to fill data gaps using closely related chemical structures and properties of various compounds. NGRA implies a combination practice of in silico and in vitro methods for animal-free testing of products and incorporating a new type of database for safety-level assessment. Overall, a range of computational approaches increasing confidence with well-curated results and leading research toward a very ethical pathway for society's benefit, such as hazard and safety assessment of a plethora of products and will continue the trend started by SCCS.

The debate over alternative testing has historically been considered primarily science-based. Furthermore, it also demands a reassessment of fundamental components of where and how regulatory toxicity studies are now done. However,

it also raises concerns about a complicated legislative framework that is not structured or equipped to reform swiftly. Overall, establishing a somewhat more fundamental perspective to regulating toxicity testing is a contemporary "Artemis," an extraction point that, if traversed, would quickly relegate several traditional procedures to an obsolete.

References

Alexander-White C, Bury D, Cronin M, Dent M, Hack E, Hewitt N et al (2022) A 10-step framework for the use of read-across (RAX) in next generation risk assessment (NGRA) for cosmetics safety assessment. Regul Toxicol Pharmacol 129:105094

Amaral R, Ansell J, Boisleve F, Cubberley R, Dent M, Hatao M, Weiss C (2018) Report for international cooperation on cosmetics regulation regulators and industry joint working group (JWG): integrated strategies for safety assessment of cosmetic ingredients: Part 2

Ankley G, Bennett R, Erickson R, Hoff D, Hornung M, Johnson R et al (2010) Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. Environ Toxicol Chem 29(3):730–741

Ashby J (1985) Fundamental structural alerts to potential carcinogenicity or non-carcinogenicity. Environ Mutagen 7(6):919–921

Bassan A, Alves VM, Amberg A, Anger LT, Auerbach S, Beilke L et al (2021) In silico approaches in organ toxicity hazard assessment: current status and future needs in predicting liver toxicity. Comput Toxicol 20:100187

Berggren E, Amcoff P, Benigni R, Blackburn K, Carney E, Cronin M et al (2015) Chemical safety assessment using read-across: assessing the use of novel testing methods to strengthen the evidence base for decision making. Environ Health Perspect 123(12):1232–1240

Berggren E, White A, Ouedraogo G, Paini A, Richarz A, Bois F et al (2017) Ab initio chemical safety assessment: a workflow based on exposure considerations and non-animal methods. Comput Toxicol 4:31–44

Bernauer U, Bodin L, Chaudhry Q, Coenraads PJ, Dusinska M, Ezendam J et al (2021) The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 11th revision, 30–31 march 2021, SCCS/1628/21. Regul Toxicol Pharmacol 127:105052

Bessems J, Paini A, Gajewska M, Worth A (2017) The margin of internal exposure (MOIE) concept for dermal risk assessment based on oral toxicity data–a case study with caffeine. Toxicology 392:119–129

Boobis A, Doe J, Heinrich-Hirsch B, Bette Meek ME, Munn S, Ruchirawat M et al (2008) IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit Rev Toxicol 38(2):87–96

Burden N, Sewell F, Andersen M, Boobis A, Chipman J, Cronin M et al (2015) Adverse outcome pathways can drive non-animal approaches for safety assessment. J Appl Toxicol 35(9): 971–975

Business Wire (2022) Global cosmetics market trends, share, size, growth, opportunities and forecast 2022–2027

Cherkasov A, Muratov EN, Fourches D, Varnek A, Baskin II, Cronin M et al (2014) QSAR modeling: where have you been? Where are you going to? J Med Chem 57(12):4977–5010

Ciallella HL, Zhu H (2019) Advancing computational toxicology in the big data era by artificial intelligence: data-driven and mechanism-driven modelling for chemical toxicity. Chem Res Toxicol 32(4):536–547

CIRS (2013) REACH and cosmetics

Comiskey D, Api AM, Barrett C, Ellis G, McNamara C, O'Mahony C et al (2017) Integrating habits and practices data for soaps, cosmetics and air care products into an existing aggregate exposure model. Regul Toxicol Pharmacol 88:144–156

Cronin M (2015) CORDIS|European Commission|integrated in silico models for the prediction of human repeated dose toxicity of cosmetics to optimise safety
Cronin M, Madden J, Richarz A (2012) The COSMOS project: a Foundation for the Future of computational modelling of repeat dose toxicity|AltTox.org
Cronin M, Enoch S, Madden J, Rathman J, Richarz A, Yang C (2022) A review of in silico toxicology approaches to support the safety assessment of cosmetics-related materials. Comput Toxicol 21:100213
Daston G, Knight D, Schwarz M, Gocht T, Thomas R, Mahony C, Whelan M (2014) SEURAT: safety evaluation ultimately replacing animal testing—recommendations for future research in the field of predictive toxicology. Arch Toxicol 89(1):15–23
de Jesus A (2020) Artificial intelligence for beauty and cosmetics-current applications. Emerj, Artificial Intelligence Research
Delrue N, Sachana M, Sakuratani Y, Gourmelon A, Leinala E, Diderich R (2016) The adverse outcome pathway concept: a basis for developing regulatory decision-making tools. Altern Lab Anim 44(5):417–429
Dent M, Amaral R, Da Silva P, Ansell J, Boisleve F, Hatao M et al (2018) Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients. Comput Toxicol 7: 20–26
Dent M, Vaillancourt E, Thomas R, Carmichael P, Ouedraogo G, Kojima H et al (2021) Paving the way for application of next generation risk assessment to safety decision-making for cosmetic ingredients. Regul Toxicol Pharmacol 125:105026
Doke S, Dhawale S (2015) Alternatives to animal testing: a review. Saudi Pharm J 23(3):223–229
EC (European Commission) (2009). Regulation No 1223/2009 of The European Parliament and of the Council on cosmetic products
ECHA (2012a) Guidance on information requirements and chemical safety assessment chapter R.19: uncertainty analysis. European Chemicals Agency, Helsinki
ECHA (2012b) Understanding REACH
ECHA (2016a) Evaluation under REACH Progress report–executive summary and recommendations to registrants
ECHA (2016b) New approach methodologies in regulatory science proceedings of a scientific workshop. Proceedings of a scientific workshop, Helsinki
ECHA (2016c) Practical guide–how to use and report (Q)SARs. Report no. 1831–6727
ECHA (2017a) The use of alternatives to testing on animals for the REACH regulation
ECHA (2017b) Read-across assessment framework (RAAF)
Ellison C, Blackburn K, Carmichael P, Clewell H, Cronin M, Desprez B et al (2019) Challenges in working towards an internal threshold of toxicological concern (iTTC) for use in the safety assessment of cosmetics: discussions from the cosmetics Europe iTTC working group workshop. Regul Toxicol Pharmacol 103:63–72
European Commission (2001) White paper: strategy for a future chemicals policy
European Commission (2004) Alternative testing methods: European research to replace and reduce animal tests
European Commission (2006) REACH regulation (EC)No1907/2006. Regulation concerning the registration, evaluation, authorisation and restriction of chemicals (REACH), establishing ECHA. Off J Eur Communities L396:1–849
European Commission (2009) Report from the commission to the European parliament and the council report on the development. Validation and legal acceptance of alternative methods to animal tests in the field of cosmetics
European Commission (2010) Directive 2010/63/EU of the European Parliament and of the Council of September 22nd 2010 on the protection of animals used for scientific purposes. Off J Eur Communities 276:33–79
European Commission (2018) 10th revision of the SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation
Fischer I, Milton C, Wallace H (2020) Toxicity testing is evolving! Toxicol Res 9(2):67–80

Garthoff B (2005) Alternatives to animal experimentation: the regulatory background. Toxicol Appl Pharmacol 207(2):388–392
Gellatly N, Sewell F (2019) Regulatory acceptance of in silico approaches for the safety assessment of cosmetic-related substances. Comput Toxicol 11:82–89
Gironde C, Dufour C, Furger C (2020) Use of LUCS (light-up cell system) as an alternative live cell method to predict human acute oral toxicity. Toxicol Rep 7:403–412
Gocht T, Berggren E, Ahr H, Cotgreave I, Cronin M, Daston G et al (2015) The SEURAT-1 approach towards animal free human safety assessment. ALTEX 32(1):9–24
Hatherell S, Baltazar MT, Reynolds J, Carmichael PL, Dent M, Li H, Ryder S, White A, Walker P, Middleton AM (2020) Identifying and characterizing stress pathways of concern for consumer safety in next-generation risk assessment. Toxicol Sci 176(1):11–33
He J, Jia Y (2021) Application of omics technologies in dermatological research and skin management. J Cosmet Dermatol 21(2):451–460
Hecker M, LaLone C (2019) Adverse outcome pathways: moving from a scientific concept to an internationally accepted framework. Environ Toxicol Chem 38(6):1152–1163
Hewitt NJ, Grégoire S, Cubberley R, Duplan H, Eilstein J, Ellison C et al (2020) Measurement of the penetration of 56 cosmetic relevant chemicals into and through human skin using a standardized protocol. J Appl Toxicol 40(3):403–415
Hirota M, Fukui S, Okamoto K, Kurotani S, Imai N, Fujishiro M, Kyotani D, Kato Y, Kasahara T, Fujita M (2015) Evaluation of combinations of in vitro sensitization test descriptors for the artificial neural network-based risk assessment model of skin sensitization. J Appl Toxicol 35(11):1333–1347
Hirota M, Ashikaga T, Kouzuki H (2018) Development of an artificial neural network model for risk assessment of skin sensitization using human cell line activation test, direct peptide reactivity assay, Keratinosensâ and in silico structure alert parameter. J Appl Toxicol 38(4): 514–526
Kabene S, Baadel S (2019) Bioethics: a look at animal testing in medicine and cosmetics in the UK. J Med Ethics Hist Med 12:15
Kim S, Lee S (2021) Deep learning approach for cosmetic product detection and classification. Comput Mater Contin 69(1):713–725
Kim K, Kwack S, Lee J, Kacew S, Lee B (2021) Current opinion on risk assessment of cosmetics. J Toxicol Environ Health Part B 24(4):137–161
Knapen D, Angrish M, Fortin M, Katsiadaki I, Leonard M, Margiotta-Casaluci L et al (2018) Adverse outcome pathway networks I: development and applications. Environ Toxicol Chem 37(6):1723–1733
Krewski D, Andersen ME, Tyshenko MG, Krishnan K, Hartung T, Boekelheide K, Wambaugh JF, Jones D, Whelan M, Thomas R et al (2010a) Toxicity testing in the 21st century: Progress in the past decade and future perspectives. Arch Toxicol 94:1–58
Krewski D, Acosta D, Anderson M, Anderson H, Bailar J, Boekelheide K et al (2010b) Toxicity testing in the 21st century: a vision and a strategy. J Toxicol Environ Health Part B 13(2–4): 51–138
Kuseva C, Schultz T, Yordanova D, Tankova K, Kutsarova S, Pavlov T et al (2019) The implementation of RAAF in the OECD QSAR toolbox. Regul Toxicol Pharmacol 105:51–61
Laroche C, Aggarwal M, Bender H, Benndorf P, Birk B, Crozier J et al (2018) Finding synergies for 3Rs–toxicokinetics and read-across: report from an EPAA partners' forum. Regul Toxicol Pharmacol 99:5–21
Lee B, Choi M, Shin I, Kim J, Choi Z, Kim K et al (2020a) Risk communication for labeling all ingredients in consumer products. J Toxic Environ Health A 83(13–14):509–524
Lee J, Kim H, Kang K, Jeong H, Song M, Tae I et al (2020b) Integration of transcriptomics, proteomics and metabolomics identifies biomarkers for pulmonary injury by polyhexamethylene guanidine phosphate (PHMG-p), a humidifier disinfectant, in rats. Arch Toxicol 94(3):887–909

Ma X, Zhang F, Wei H, Xu L (2021) Deep learning method for makeup style transfer: a survey. Cogn Robot 1:182–187
Madden J, Tan Y, Blaauboer B, Paini A (2020a) Development and application of physiologically-based kinetic (PBK) models. Comput Toxicol 13:100116
Madden JC, Enoch SJ, Paini A, Cronin MT (2020b) A review of in silico tools as alternatives to animal testing: principles, resources and applications. Altern Lab Anim 48(4):146–172
Meigs L (2018) Animal testing and its alternatives–the most important omics is economics. ALTEX 35:275–305
Merenyi S (2018) REACH: regulation(EC) no 1907/2006. 152–158
Munro I, Ford R, Kennepohl E, Sprenger J (1996) Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. Food Chem Toxicol 34(9): 829–867
Nambiar K (2021) 3 applications of AI in the cosmetic industry
NAS (2007) Toxicity testing in the twenty-first century: a vision and a strategy. National Academies Press, Washington DC
NAS (2012) Exposure science in the 21st century: a vision and a strategy. National Academies Press, Washington DC
NAS (2017) Using 21st century science to improve risk-related evaluations. National Academies Press, Washington, DC
National Research Council (2007) Toxicity testing in the 21st century: a vision and a strategy. National Academies Press, Washington, DC
OECD (2011a) Series on testing and assessment no. 138: report of the workshop on using mechanistic information in forming chemical categories (176pp)
OECD (2011b) Series on testing and assessment no. 139: report of the expert consultation on scientific and regulatory evaluation of organic chemistry based structural alerts for the identification of protein-binding chemicals (100pp)
OECD (2012a) OECD series on testing and assessment no 168: the adverse outcome pathway for skin sensitisation initiated by covalent binding to proteins. Part 2: use of the AOP to develop chemical categories and integrated assessment and testing approaches.(46pp)
OECD (2012b) OECD series on testing and assessment no. 168: the adverse outcome pathway for skin sensitisation initiated by covalent binding to proteins. Part 1: scientific evidence (59pp)
OECD (2013) Guidance document on developing and assessing adverse outcome pathways. Environment, health and safety publications. Series on testing and assessment, no. 184, Vol. 6
OECD (2016a) Guidance document on the reporting of defined approaches to be used within integrated approaches to testing and assessment. Series on testing and assessment no. 255
OECD (2016b) Users' handbook supplement to the guidance document for developing and assessing adverse outcome pathways. Environment, health and safety publications, series on testing and assessment no. 233
OECD (2017a) Guidance document on the reporting of defined approaches and individual information sources to be used within integrated approaches to testing and assessment (IATA) for skin sensitisation. Series on testing and assessment no. 256
OECD (2017b) Adverse outcome pathways, molecular screening and toxicogenomics
Patlewicz G, Cronin M, Helman G, Lambert J, Lizarraga L, Shah I (2018) Navigating through the minefield of read-across frameworks: a commentary perspective. Comput Toxicol 6:39–54
Pirih N, Kunej T (2017) Toward a taxonomy for multi-omics science? Terminology development for whole genome study approaches by omics technology and hierarchy. OMICS 21(1):1–16
Potts RO, Guy RH (1992) Predicting skin permeability. Pharm Res 9(5):663–669
Pouillot A, Polla B, Polla A (2009) REACH: impact on the US cosmetics industry? J Cosmet Dermatol 8(1):3–7
REACH (2012) Chemicals–environment—European Commission
REACH (2022) Health and safety authority
Rise for Animals (2022) Seeking justice for animals in labs

Rogiers V, Benfenati E, Bernauer U, Bodin L, Carmichael P, Chaudhry Q et al (2020) The way forward for assessing the human health safety of cosmetics in the EU–workshop proceedings. Toxicology 436:152–421

Sachana M (2018) Approaching the development of alternative testing methods using information available in the adverse outcome pathway knowledgebase (AOP-KB). Toxicol Lett 295:S41

Safford B, Api AM, Barratt C, Comiskey D, Daly EJ, Ellis G et al (2015) Use of an aggregate exposure model to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products. Regul Toxicol Pharmacol 72(3):673–682

Safford B, Api AM, Barratt C, Comiskey D, Ellis G, McNamara C et al (2017) Application of the expanded Creme RIFM consumer exposure model to fragrance ingredients in cosmetic, personal care and air care products. Regul Toxicol Pharmacol 86:148–156

Sakuratani Y, Horie M, Leinala E (2018) Integrated approaches to testing and assessment: OECD activities on the development and use of adverse outcome pathways and case studies. Basic Clin Pharmacol Toxicol 123:20–28

SCCS (2016) SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation 9th revision. Revision of April 25th 2016

SCCS (2018) SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation 10th revision, 24–25

Schultz T, Amcoff P, Berggren E, Gautier F, Klaric M, Knight D et al (2015) A strategy for structuring and reporting a read-across prediction of toxicity. Regul Toxicol Pharmacol 72:586–601

Schultz T, Dimitrova G, Dimitrov S, Mekenyan O (2016) The adverse outcome pathway for skin sensitisation: moving closer to replacing animal testing. Altern Lab Anim 44(5):453–460

SciForce (2019) Machine learning: changing the beauty industry

Sheehan KB, Lee J (2014) What's cruel about cruelty-free: an exploration of consumers, moral heuristics, and public policy. J Anim Ethics 4(2):1

Sturla S, Boobis A, FitzGerald R, Hoeng J, Kavlock R, Schirmer K et al (2014) Systems toxicology: from basic research to risk assessment. Chem Res Toxicol 27(3):314–329

Tanner B (2022) Cosmetic testing–microchem laboratory

Taylor K, Rego Alvarez L (2020) Regulatory drivers in the last 20 years towards the use of in silico techniques as replacements to animal testing for cosmetic-related substances. Comput Toxicol 13:100–112

Thomas R, Philbert M, Auerbach S, Wetmore B, Devito M, Cote I et al (2013) Incorporating new technologies into toxicity testing and risk assessment: moving from 21st century vision to a data-driven framework. Toxicol Sci 136(1):4–18

Tintó-Moliner A, Martin M (2020) Quantitative weight of evidence method for combining predictions of quantitative structure-activity relationship models. SAR QSAR Environ Res 31(4):261–279

Tollefsen K, Scholz S, Cronin M, Edwards S, de Knecht J, Crofton K et al (2014) Applying adverse outcome pathways (AOPs) to support integrated approaches to testing and assessment (IATA). Regul Toxicol Pharmacol 70(3):629–640

Tozer S, O'Mahony C, Hannah J, O'Brien J, Kelly S, Kosemund-Meynen K, Alexander-White C (2019) Aggregate exposure modelling of vitamin a from cosmetic products, diet and food supplements. Food Chem Toxicol 131:110–549

Turley A, Isaacs K, Wetmore B, Karmaus A, Embry M, Krishan M (2019) Incorporating new approach methodologies in toxicity testing and exposure assessment for tiered risk assessment using the RISK21 approach: case studies on food contact chemicals. Food Chem Toxicol 134: 110–819

Umer S, Mohanta P, Rout R, Pandey H (2020) Machine learning method for cosmetic product recognition: a visual searching approach. Multimed Tools Appl 80(28–29):34997–35023

USEPA (2014) Next generation risk assessment: incorporation of recent advances in molecular, computational, and systems biology. National Center for environmental assessment, Office of Research and Development. U.S. Environmental Protection Agency, Washington DC

US-FDA (2022) Product testing of cosmetics
van Delft J, Mathijs K, Polman J, Coonen M, Szalowska E, Verheyen G et al (2014) Hepatotoxicity screening on in vitro models and the role of omics. In: Kleinjans J (ed) Toxicogenomics-based cellular models. Academic Press, Cambridge, pp 193–212
Van Der Wielen A (2007) REACH: next step to a sound chemicals management. J Expo Sci Environ Epidemiol 17(1):S2–S6
Villalobos A, Tenneriello B, Koppisch E, Fagan J (2014) Cosmetic testing on animals
Villeneuve D (2015) In response: the path forward for the adverse outcome pathway framework-a regulatory perspective. Environ Toxicol Chem 34(9):1938–1940
Villeneuve D, Crump D, Garcia-Reyero N, Hecker M, Hutchinson T, LaLone C et al (2014) Adverse outcome pathway (AOP) development I: strategies and principles. Toxicol Sci 142(2):312–320
Vinardell M, Mitjans M (2017) Alternative methods to animal testing for the safety evaluation of cosmetic ingredients: an overview. Cosmetics 4(3):30
Vinken M, Kramer N, Allen T, Hoffmans Y, Thatcher N, Levorato S et al (2020) The use of adverse outcome pathways in the safety evaluation of food additives. Arch Toxicol 94(3):959–966
White E (2022) An analysis of animal testing in beauty products and its ethicality
Williams F, Rothe H, Barrett G, Chiodini A, Whyte J, Cronin M et al (2016) Assessing the safety of cosmetic chemicals: consideration of a flux decision tree to predict dermally delivered systemic dose for comparison with oral TTC. Regul Toxicol Pharmacol 76:174–186
Wilm A, Stork C, Bauer C, Schepky A, Kühnl J, Kirchmair J (2019) Skin doctor: machine learning models for skin sensitization prediction that provide estimates and indicators of prediction reliability. Int J Mol Sci 20(19):33–48
Wittwehr C, Munn S, Landesmann B, Whelan M (2015) Adverse outcome pathways knowledge base (AOP-KB). Toxicol Lett 238(2):S309
Wittwehr C, Aladjov H, Ankley G, Byrne H, de Knecht J, Heinzle E et al (2016) How adverse outcome pathways can aid the development and use of computational prediction models for regulatory toxicology. Toxicol Sci 155(2):326–336
Worth A, Cronin M, Enoch S, Fioravanzo E, Fuart-Gatnik M, Pavan M, Yang C (2012) Applicability of the threshold of toxicological concern (TTC) approach to cosmetics–preliminary analysis. Eur Union 10:5059
Wu Y, Wang G (2018) Machine learning based toxicity prediction: from chemical structural description to transcriptome analysis. Int J Mol Sci 19(8):23–58
Yamada T, Ashikaga T, Kojima H, Hirose A (2020) Challenge for adverse outcome pathway (AOP)-based chemical safety assessment. Yakugaku Zasshi 140(4):481–484
Yang C, Barlow S, Muldoon Jacobs K, Vitcheva V, Boobis A, Felter S et al (2017) Thresholds of toxicological concern for cosmetics-related substances: new database, thresholds, and enrichment of chemical space. Food Chem Toxicol 109:170–193
Yang C, Cronin M, Arvidson K, Bienfait B, Enoch S, Heldreth B et al (2021) COSMOS next generation–a public knowledge base leveraging chemical and biological data to support the regulatory assessment of chemicals. Comput Toxicol 19:100–175
Zimbardi D (2018) Gene expression screening to identify activation profiles in skin after exposition to cosmetic ingredients. In: 2nd pan-American for conference alternative methods. Natura innovation, Cajamar, SP