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Review

Computational Methods as Part of Scientific Research in Cosmetic Sciences—Are We Using the Opportunity?

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Abstract: In the field of the cosmetic industry, significant efforts are made to develop methods that are not only cost effective and time effective but are also environmentally friendly and cruelty free. Cosmetic tests using in vivo animal models are currently banned in the European Union. To fulfil regulatory requirements, new approach methodologies (NAMs) are implemented, and thereupon, in silico techniques have constantly acquired significance. This review aimed to show the general picture of the available computational methods and approaches, give some examples of their applications, present capabilities and limitations, and propose the way forward. The general information about in silico modelling and examples of its usage in the context of cosmetics and its legal regulation are presented. The review is divided with a focus on three endpoints of interest: (1) safety assessment, (2) exposure assessment, and (3) formulation characterization. With this comprehensive analysis, we try to answer the question as to whether we are using the opportunity.

Keywords: cosmetics; in silico models; computational models; quantitative structure–activity relationship; quantitative structure–property relationships; physiologically based kinetic models; safety; non-animal methods; formulation optimization

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1. Introduction

The cosmetics industry generates significant revenue and is characterized by steady sales growth [1]. There are, however, some trends that suggest that the market, specifically in highly developed countries, is changing, and more focus is put on environmentally friendly and cruelty-free products [2,3]. This requires investment in R&D and an active search for alternative testing methods that are scientifically robust, economically plausible, and most importantly, acceptable to the regulatory bodies. One of the branches of science that can still be seen as an alternative to gold standard methods—which are mostly in-vitro-based models—includes computational methods and mathematical algorithms [4]. Recognition and interest in the possible use of QSARs and other mathematical models in cosmetics science has evolved with the advent of the animal testing ban. Even considering the current hype around tools based on Machine Learning algorithms (sometimes called 'Artificial Intelligence'), the in-depth understanding and acceptance of methods based on mathematics is limited [5–7].

This review did not aim to run a detailed query on the computational models developed and utilized for cosmetics at various stages of their development and manufacturing. Neither did we try to provide a comprehensive description of all scientific reports where such methods were presented. The aim was rather to show the general picture of the

available computational methods and approaches, give some examples of their applications, present capabilities and limitations, and propose the way forward. Moreover, this review is focused on the European perspective only, while the regulatory approaches vary worldwide [8] and the global perspective may differ.

2. Modeling and Simulation—Various Modeling Approaches, Dependent Variable Character, and Various Input Data

Mechanistic and empirical model building take fundamentally different approaches to model development and parameterization. Empirical models are focused on describing the observed data with the underlying assumptions of no insights into the mechanisms that led to the occurring data being analyzed. In general, relatively simple equations derived from statistics and regression analysis are used. Model development is relatively straightforward and not time consuming in regard to the condition of access to measured data for the endpoint of interest. Data quality and amount are critical for model building and potential utilization. Empirical models are used predominantly for interpolation and every extrapolation beyond the observed data should be carried out with extreme caution. In the drug development realm, examples of empirical models are allometric scaling systems, which allow pharmacokinetic (PK) parameters to be scaled across various species. Mechanistic models make an attempt to incorporate into the model known factors and natural laws (chemical, physical, biological) about the systems surrounding the data [9]. With that, the mechanistic models can be used to extrapolate beyond the data space used for the model development. As the model development requires good understanding of the basic phenomena, it can be time and effort consuming, but once the model is implemented and validated, its use is effortless. Similarly, as in the empirical models, data quality is of importance; however, in this case, its quantity is not that critical.

The character of the model as well as the algorithm applied for model building depend on the character of the dependent (modelled) variable. For categorical data, regardless of the number of classes, algorithms allowing for classification (or clustering) are applied. An example of categorical data is binary sets where the modelled variable can be classified into two classes—positive (i.e., toxic) or negative (i.e., safe). For a continuous variable (variable for which we can assume an infinite number of real values within a defined interval), the regression type of models needs to be applied. An example of such an endpoint is the skin partition coefficient, permeability, flux, or diffusion in the tissue of interest.

Apart from the above-mentioned data quality, the scientific character and robustness of the input data are of critical importance. For most of the problems described in the current manuscript, the structural description and physicochemical parameters of the substances of interest are used as the input (independent) information for empirical models. However, considering the heterogeneity of the input data, resulting from experimental values measured in different labs and under different conditions, some pre-processing might be necessary.

3. Cosmetic Sciences and Cosmetic Product Development—Endpoints of Interest

3.1. Safety Assessment

Cosmetic products need to undergo extensive testing to determine if they meet regulatory standards and consumer expectations before they can be launched for sale. The most important part of this process is the safety assessment. The cosmetic industry has been undergoing a substantial paradigm shift guided by ethical considerations and legislation regulations changes in 2003 in the 7th Amendment (Directive 2003/15/EC) to the European Cosmetics Directive (76/768/EEC). The information currently required to prove product safety after the complete ban on animal testing is specified in the European Cosmetic Regulation N°1223/2009 [10], and the Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation published by the Scientific Committee for Consumer Safety (SCCS) [11]. Moreover, to ensure consumer safety, the cosmetics effectiveness and safety claims have to comply with Regulation N°655/2013 [12]. The expected advent of

announced legislative changes intensified an upsurge of interest in alternatives to animal testing, and many non-animal approaches have been developed, validated, and accepted by the regulatory community. These include a wide range of in vitro, ex vivo, in chemico, and in silico methods as well as read-across approaches, plus human volunteer research.

The most relevant toxicological endpoints contributing to the safety assessment of cosmetic ingredients and products encompass, but are not limited to, skin sensitization potential, skin and eye irritation, endocrine-disrupting potential, and genotoxicity. For each of these endpoints, several new approach methods (NAMs) that offer ethical, rapid, and cost-effective solutions can be applied (Table 1). These include in vitro experiments and predictive in silico models and tools. The latter, namely in silico approaches, are based on structure–activity relationships (SARs), quantitative structure–activity relationships (QSARs), and quantitative mechanistic modelling (QMM). There are also tools for the read-across of data from structurally or functionally similar substances and expert systems [13–17].

Table 1. Examples of New Approach Methods (NAMs) for cosmetic products and ingredients toxicity endpoints.

Conditions/Method Type	Test/Software
Sensitization	Skin sensitization is an induction of a specific immunological reaction following contact with the agent penetrating into the epidermis, which can provoke allergic contact dermatitis upon subsequent exposure.
In vitro	
Covalent binding of the chemical to proteins of the skin	Direct Peptide Reactivity Assay (DPRA) Amino acid Derivative Reactivity Assay (ADRA) Kinetic Direct Peptide Reactivity Assay (kDPRA)
Keratinocyte activation	ARE-Nrf2 Luciferase KeratinoSens method ARE-Nrf2 luciferase LuSens EpiSensA SENS-IS
Dendritic cell activation	Human Cell Line Activation (h-CLAT) U937 Skin Sensitization Test (U-SENS) Interleukin-8 Reporter Gene Assay (IL8-Luc assay) Genomic Allergen Rapid Detection (GARDTM) for the detection of skin sensitization (GARDskinTM)
In vivo	
	ITS-SkinSensPred Derek Nexus OECD QSAR Toolbox ToxTree UL's REACHAcros Danish QSAR Database (Consensus model from ACDLabs, Leadscope, CASE Ultra, and SciQSAR) TIMES-SS CASE Ultra, MultiCASE VEGA SkinSensPred (majority vote and decision tree model; similarity) Pred-skin (QSAR+Baeysian model)
Skin/Eye Corrosion and Irritation	Corrosion is irreversible (necrotic) and irritation is a reversible damage to the skin, following the application of a test substance for up to 4 h. Eye irritation is defined by the occurrence of changes in the eye in response to the application of a test substance that are fully reversible within 21 days of application.

Table 1. *Cont.*

Conditions/Method Type	Test/Software
In vitro skin	
Skin corrosion	Rat Skin Transcutaneous Electrical Resistance (TER) Reconstructed human Epidermis (RhE) Test Method (EpiSkin™, Lyon, France, EpiDerm™ SCT (EPI-200), Ashland, MA, USA SkinEthic™ RHE, Lyon, France, epiCS® and LabCyte EPI-MODEL24) Membrane Barrier Test Method (OECD TG 435), including the Corrositex® test method
Skin irritation	Reconstructed Human Epidermis (RhE) Test Method (EpiSkin™, EpiDerm™ SIT (EPI-200), SkinEthic™ RHE and LabCyte, San Jose, CA, USA EPI-MODEL24SIT, EpiCS, Skin+®, KeraSkin™, Seoul, Republic of Korea)
In vitro eye	
Organotypic test methods	Bovine Cornea Opacity Permeability (BCOP) Isolated Chicken Eye (ICE) Isolated Rabbit Eye Hen's Egg Test on Chorioallantoic Membrane (HET-CAM)
Cytotoxicity and cell-function-based in vitro tests	Short Time Exposure (STE) test method using a rabbit corneal cell line Fluorescein Leakage (FL) test using epithelial monolayer of MDCK kidney cells
Reconstructed human tissue (RhT)-based test methods	Reconstructed Human-Cornea-like Epithelium (RhCE SkinEthic™ HCE Time to Toxicity Vitrigel-EIT
In vitro macromolecular test method	Ocular Irritection (OI®)
In silico	
	TOPKAT MultiCASE Derek Nexus Bundesinstitut für Risikobewertun (BfR) decision support system HazadExpert STopTox
Endocrine Disruption	Interaction, interference, or disruption of the function of the endocrine system
In vitro	
	Estrogen or androgen receptor binding affinity Estrogen, retinoid receptor transactivation Yeast estrogen screen Androgen receptor transcriptional activation Rapid androgen disrupter activity reporter assay Steroidogenesis Aromatase Assay Thyroid disruption assays (e.g., thyroperoxidase inhibition, transthyretin binding)
	ADMET Predictor™ MetaDrug™ VEGA Online Chemical Modelling Environment (OCHEM) OECD QSAR Toolbox MultiCASE ERBA QSAR US EPA's rtnER
Genotoxicity	Induced by several mechanisms of alteration of the structure, information content, or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or that alter its replication in a non-physiological manner

Table 1. *Cont.*

Conditions/Method Type	Test/Software
In vitro	
	Ames Test
	TransGenic Rodent (TGR) mutagenicity assays
	—mutagenicity assays based on immortalized cell lines or primary hepatocytes from the MutaMouse or lacZ Plasmid Mouse
	Phosphatidylnositol glycan class A gene (Pig-a)
	Genome-wide loss-of-function screening, mutation characterization by next generation sequencing, and fluorescence-based mutation detection
	3D Tissues
	High-Information-Content assay
In silico	
	LAZAR
	Danish QSAR database
	US-EPA's Toxicity Estimation Software Tool (T.E.S.T.)
	OECD QSAR Toolbox
	ToxRead
	VEGA QSAR platform
	ToxTree
	OpenTox for carcinogenicity
	OncoLogic (US EPA)
	SciQSAR
	TopKat
	CASE Ultra
	Leadscope
	Derek Nexus

The in silico methods list is non-exhaustive and presents chosen examples of models and systems.

3.2. Exposure Assessment

A thorough investigation of exposure is an integral aspect of introducing a new cosmetic product to the market. While chemical kinetics assessment primarily focuses on skin permeation, it is not confined solely to this aspect. The Cosmetic Product Safety Report (CPSR) is required before marketing a cosmetic product in the European Union. It encompasses an analysis of exposure related to the actual expected product use, considering factors such as the site of application, surface area, applied quantity, duration and frequency of use, normal and reasonably foreseeable exposure route(s), and the exposed population [10]. Toxicokinetic analysis should involve the possible exposure via inhalation and the oral route, or other if feasible (e.g., eye, vaginal, rectal). Even though the exposure is often negligible, this must be taken into consideration, especially in the case of products such as aerosols or powders for inhalation, and lipstick, toothpaste, or mouthwash for use via the oral route [11].

According to the SCCS Guidance For The Testing Of Cosmetic Ingredients And Their Safety Evaluation, exposure should be calculated using appropriate models [11]. External dermal exposure (E_{dermal}) expressed in mg/day can be calculated by multiplication of the concentration/fraction of a substance in a product (C_x), amount of product that is applied/received per day (q), and retention factor (F_{ret}). Both q and F_{ret} are specific to the product category. Furthermore, dermal absorption should be tested in vitro following a combination of the OECD Test Guideline 428 and the "Basic Criteria" outlined in the SCCS guidelines [18]. Traditionally, systemic exposure was tested with the use of in vivo models. However, the use of living animals in cosmetic studies is currently prohibited in Europe. E_{dermal} can be used for assessment of the systemic exposure dose by multiplying with the chemical and route-specific uptake rate, and normalization by bodyweight. It can also be assessed using appropriate in silico models, mainly physiologically based kinetic (PBK) models [19].

The in vitro permeation test (IVPT) should be conducted using excised human or pig skin employing a diffusion cell method. The study endpoint should include the amount of tested substance in the receptor solution, its distribution in the different skin layers (if applicable), and the residual amount of chemicals on the membrane. The results should provide information on substance recovery, the absorption profile, and tabulated absorption data, expressed as the rate, amount, or percentage [18]. These studies, in harmonized conditions, demonstrate a good correlation with in vivo observations [20]. In vitro studies are suitable for testing the skin permeation of cosmetic ingredients under single-dose conditions. However, their utility is limited when assessing different dosing scenarios, such as exposure in long-term repeated dosing. Although this gap has been addressed by in vivo studies, those are now commonly replaced by in silico methods [21]. These methods can be implemented to predict local skin distribution similarly to in vitro studies, but they can extend their ability to simulate various dosing regimens [22]. Moreover, when integrated with PBK models, they can be used to predict systemic fate [19]. Various parameters are used to describe dermal absorption, and the most common are shown in Table 2.

Table 2. Most common parameters used to describe dermal absorption.

Name	Units	Comments
Permeability coefficient (Per)	$cm \times h^{-1}$	
Partition coefficient (Kp)	-	E.g., skin:formulation, formulation:stratum corneum, stratum corneum:viable epidermis, viable epidermis:dermis, stratum corneum lipids:water, stratum corneum proteins:water
Diffusion coefficients (D)	$cm^2 \times h^{-1}$	E.g., in stratum corneum, stratum corneum lipids, viable epidermis, dermis, sebum, buffer
Flux (J)	$mg \times cm^{-2} \times h^{-1}$	
Amount in receptor solution	$\mu g \times cm^{-2}$	From IVPT studies
Amount in the skin	$\mu g/cm^2$	Full skin or in selected layers (stratum corneum, viable epidermis, dermis)
Systemic concentration	$\mu g/mL$	Plasma or specific organ concentration

Permeability coefficient (Per) and flux (J) are often used to evaluate dermal permeation. There are numerous quantitative structure–property relationship (QSPR) models developed to estimate Per and J based on physicochemical descriptors and structural properties of the molecule (Table 3) [23]. However, OECD guidance notes on dermal absorption indicate their limited applicability [24,25]. Authors have pointed out several problems, such as the limited data used as a training set and often lack of information about the experimental condition under which the experimental results have been obtained. Moreover, models are usually simple and do not account for the influence of the vehicle and type of formulation, with some exceptions such as the model of Riviere and Brooks (2005), which enables prediction of permeability from complex chemical mixtures [26] Per is often applied as it is assumed to be constant over the concertation range. It is important to note that there are various abbreviations for the permeability coefficient in the literature, and one commonly used is “Kp”, which may be confusing, as the same is used for the partition coefficient. Referring to the OECD guidelines, flux can be applicable when real exposure is like infinite dosing conditions, for example, topically applied products left on the skin. Nevertheless, real-life exposure is often similar to finite dosing. Furthermore, flux calculated in vitro is based on the amount of chemical permeated to the receptor solution and does not reflect the amount retained in the skin [24]. Some authors propose models for simulations reflecting real-life finite dosing conditions of applying cosmetics [27].

Table 3. Example of quantitative structure–property relationship (QSPR) models used to predict permeability coefficients (Per) or flux (J).

Authors/Model	Descriptors	Output	Source
Potts and Guy, 1992	$k_{o/w}$ [a], MW [b] or MV [c]	Per	[28]
Moss and Cronin, 2002	$\log k_{o/w}$ [a], MW [b]	Per	[29]
Barratt, 1995	$\log k_{o/w}$ [a], MV [c], melting point	Per	[30]
Frasch, 2002	$\log k_{o/w}$ [a], MW [b]	Per	[31]
Wilschut, 1995 (Modified Robinson Model)	$\log k_{o/w}$ [a], MW [b]	Per	[32]
Fitzpatrick, 2004	$\log k_{o/w}$ [a], MW [b]	Per	[33]
Buchwald and Bodor, 2001	A [d], N [e]	Per	[34]
Magnusson, 2004	MW [b], solute melting point	J_{max}	[35]
Milewski-Stinchcombe, 2012	$\log k_{o/w}$ [a], MW [b], solute melting point	J_{max}	[36]
Roberts-Sloan,1999	MW [b], $\log S_{IPM}$ [f], $\log S_{PG}$ [g]	J	[37]
Cronin, 1999	$\log k_{o/w}$ [a], molecular mass	Per	[38]
Patel, 2002	$\log k_{o/w}$ [a], MW [b], ABSQon [h], SsssCH [i]	Per	[39]
Abraham, 1995	Solute dipolarity/polarizability, solute hydrogen bond acidity, solute hydrogen bond basicity, McGowan characteristic molecular volume, excess molar refraction	Per	[40]
Mitragotri, 2002	$\log k_{o/w}$ [a], solute molecular radius	Per	[41]
Fujiwara, 2003	$\log k_{o/w}$ [a], MW [b]	Per	[5]
Khajeh and Modarress, 2014	EEig15r [j], $\log k_{o/w}$ [a], Neoplastic-80 [k]	Per	[42]
Baba, 2017	15 molecular descriptors	Per	[43]
Chen, 2018	$\log k_{o/w}$ [a], D/Dr10 [l], T(O..Cl) [m], Neoplastic-80 [k]	Per	[44]
Rezaei, 2019	GRid-INdependent Descriptors	Per	[45]
Wu, 2022	$\log k_{o/w}$ [a], MV [c], χ [n], Jurs_PPSA_1 [o]	Per	[46]
Waters and Quah, 2022	$\log k_{o/w}$ [a], MV [c], TPSA [p]	Per	[47]
The Dermal Permeability Coefficient Program (DERMWIN)	$\log k_{o/w}$ [a], MW [b]	Per	Module available in the EPI Suite package developed by the EPA's Office of Pollution Prevention Toxics and Syracuse Research Corporation

[a] $k_{o/w}$—n-octanol/water partition coefficient; [b] MW—molecular weight; [c] MV—molecular volume; [d] A—effective van der Waals molecular volume; [e] N—parameter related to the hydrogen bonds formed at the acceptor sites of the solute molecule; [f] $\log S_{IPM}$—log solubilities in isopropyl myristate; [g] $\log S_{PG}$—log solubilities in propylene glycol; [h] ABSQon—sum of absolute charges on oxygen and nitrogen atoms; [i] SsssCH—sum of E-state indices for all methyl groups; [j] EEig15r—Eigenvalue 15 from edge adjacency matrix weighted by resonance integrals; [k] Neoplastic-80—Ghose–Viswanadhan–Wendoloski antineoplastic-like index at 80%; [l] D/Dr10—distance/detour ring index of order 10; [m] T(O..Cl)—sum of topological distances between O..Cl; [n] χ—molecular connectivity index of order zero; [o] Jurs_PPSA_1—partial positive surface area; [p] TPSA—topological surface area.

To enhance the understanding of chemical skin permeation, the incorporation of the partition coefficient (Kp) and diffusion coefficients (D) is beneficial. These parameters are useful for assessing local exposure and serve as inputs for predicting systemic exposure [48–50]. Although both Kp and D can be estimated using results from in vitro experiments, there are various in silico models, as outlined in Table 4, that are available to facilitate their estimation. These parameters offer insight into chemical deposition in different skin layers, enabling mechanical descriptions of the dermal permeability process. However, it is important to note that the limitation of such a model is that the partition coefficient between the vehicle and SC can be predicted only for water as a vehicle.

Table 4. Examples of mathematical models used to predict partition coefficient (kp) and diffusion coefficients (D) [49].

Authors	Input (Independent) Parameters	Output	Source
Hansen, 2013	$logk_{o/w}$ [a]	SC lipid: water Kp	[48]
Nitsche, 2006	$logk_{o/w}$ [a]	SC lipid: water Kp	[51]
Raykar, 1988	$logk_{o/w}$ [a]	SC lipid: water Kp	[52]
Yang, 2018	$logk_{o/w}$ [a], pH, f_{ni} [b], f_{CAT} [c]	Sebum: water Kp	[53]
Valiveti, 2008	$logk_{o/w}$ [a]	Sebum: water Kp	[54]
Chen, 2015	SC lipid: water kp, $f_{u,plasma}$ [d], $f_{ni,VE}$ [e]	SC lipid: viable epidermis Kp	[55]
Kretsos, 2008	Amount desorbed from tissue, density	Dermis: water Kp	[56]
Shatkin and Brown, 1991	$logk_{o/w}$ [a], $f_{fat,SC}$ [f], $f_{fat,VE}$ [g]	SC lipid: viable epidermis Kp	[57]
Shatkin and Brown, 1991	[h] $f_{fat,D}$, [i] $f_{fat,blood}$	Dermis: blood Kp	[57]
Patel, 2022	[j] $f_{ni,dermis}$, sebum: water kp, lipid: water kp	Dermis: sebum Kp	[49]
Johnson, 1996	MW [k], skin temperature	D SC lipid, D sebum	[58]
Mitragotri, 2003	Molecular radius	D SC lipid	[59]
Wang, 2006	MW [k]	D SC lipid	[60]
Guy, 1982	Transport distance, time	D viable epidermis	[61]
Clarke, 2019	MW [k]	D dermis	[62]
Yang, 2019	MW [k]	D sebum	[63]

[a] ko/w—n-octanol/water partition coefficient; [b] f_{ni}—fraction of the drug which is in non-ionized form for current pH; [c] f_{CAT}—fraction of the drug which is cation form for the current pH; [d] $f_{u,plasma}$—fraction unbound in plasma, [e] $f_{ni,VE}$—non−ionized fraction in VE at pH 7; [f] $f_{fat,SC}$—lipid fraction in SC; [g] $f_{fat,VE}$—lipid fraction on viable epidermis; [h] $f_{fat,D}$—lipid fraction in dermis, [i] $f_{fat,blood}$—lipid fraction in blood; [j] $f_{ni,dermis}$—non−ionized fraction in dermis; [k] MW—molecular weight.

Data generated with the use of in silico QSPR models or in vitro methods can be effectively utilized for assessing local or systemic exposure, employing PBK or physiologically based toxicokinetic (PBTK) models [64]. The use of physiologically based mechanistic models is generally accepted in the pharmaceutical industry in both drug discovery and generic formulation development [65–67]. In 2019, nearly half of new approvals included a PBPK analysis [68]. Nevertheless, this approach can also be successfully implemented in cosmetic development [69]. The systematic review of PBK models published in 2021 contains 181 models of substances applied topically on the skin and 82 administered via dermal injections [70].

PBK/PBTK are mechanistic or semi-mechanistic models, which integrate description of the system (e.g., body or individual organ as skin), expressed as a set of interconnected compartments with detailed information on a tested chemical and application conditions (such as amount, exposure duration, dosing frequency). Their advantage over classical toxicokinetic approaches lies in their ability to predict dynamic outputs, such as concentration–time plots in specific compartments. PBK models are often implemented to predict local or systemic exposure in the human body. However, some of them, such as the standalone multi-phase, multi-layer mechanistic dermal absorption (MPML MechDermA) model, can also be used for permeability prediction in IVPT conditions [49]. Therefore, PBK models can be useful at various stages of new cosmetic product development.

Cheruvu et al. (2022), in their review, listed various PBK software for predicting dermal and systemic exposure of topically applied chemicals, including the MechDermA model implemented in the Simcyp® platform, the Transdermal Compartmental Absorption and Transit (TCAT™) model available in Gastroplus®, and toxicokinetic software such as EPA's Stochastic Human Exposure and Dose Simulation (SHEDS), U.S. EPA. Swimmer Exposure Assessment Model (SWIMODEL), RISKOFDERM, EUROPOEM II, and DREAM [71]. In a review by Grégoire et al. (2021), the accuracy and limitations of five skin penetration models were assessed, including DSkin, TCAT™, Simcyp Certara Population-Based Simulator, model introduced by the University of Surrey, and the CDC "Finite Dose Skin Permeation Calculator" [22]. The analysis revealed that all five models provided reasonable predictions for dermal delivery, encompassing the amount of chemical in the epidermis, dermis, and

receptor fluid. Three models (TCAT, Surrey, and CDC models) were employed to simulate receptor fluid kinetics, and all three showed good predictability. However, the authors noted poor predictability regarding the amounts of chemicals in the epidermis and dermis. They also pointed out the need for further development, particularly focusing on the influence of the vehicle, such as the accurate prediction of evaporation.

Moxon et al., (2020) studied the utilization of the PBK approach to address the issue of limited methods for systemic exposure assessment [64]. They developed a framework for predicting the exposure of new ingredients applied dermally and demonstrated its utility in building models of three chemicals (coumarin, caffeine, and sulforaphane) in four product types (kitchen cleaner liquid, face cream, shampoo, and body lotion).

To enhance prediction accuracy, a robust validation process is essential. However, the prohibition of using living animals in cosmetic studies significantly limits the availability of in vivo data for validation purposes [72]. This issue has been addressed in the OECD Guidance Document on the Characterisation, Validation and Reporting of PBK Models for Regulatory Purposes [73]. In cases where in vivo data for a tested substance is unavailable, a read-across framework can be implemented, which involves using substance analogues to bridge data gaps and support model validation. When relevant empirical in vivo data are lacking for certain chemicals, a detailed examination of the input parameters, including a global sensitivity analysis, should be implemented to assess model reliability.

Alexander-White et al., (2022) proposed a 10-step framework for the use of a read-across approach in cosmetic safety assessment [74]. It encompasses structured instructions for developing a PBK model, with a list of useful data sources. This framework was applied to study the safety of parabens [75] and caffeine as cosmetic ingredients [76]. The PBK modeling approach was successfully applied for predicting plasma concentration time profiles of three highly lipophilic and highly protein bound UV filters (octyl methoxycinnamate, octocrylene, and 4-methylbenzylidene camphor), with the parametrization based entirely on data generated in vitro and/or in silico [77]. Another example of implementing PBK modeling in dermal exposure assessment is a health risk analysis from dermal contact with bisphenols [78].

3.3. Formulation Characterization

The final cosmetic product is subject to several quality tests. The attributes that are evaluated may be divided into three groups, i.e., functional including safety, exposure, and stability, sensorial such as texture, appearance, or smell, and related to the efficacy. The EU Regulation 1223/2009 [10,79] defines the following main types of testing for cosmetic products:

1. Physicochemical properties;
2. Stability in reasonably foreseeable storage conditions and compatibility testing;
3. Microbiological quality and challenge testing.

Final product safety is usually inferenced from the safety profile of its individual substances. However, a skin compatibility test should be conducted even if safe substances were used, while the whole formulation rather than individual ingredients determines local tolerance. Also, product safety evaluation is highly related to the condition of use since it is dependent on the amount of substance that can be absorbed, ingested, or inhaled and, thus, anticipated human exposure needs to be considered.

As physical and chemical property assessment is a part of good manufacturing practice (GMP), it is necessary to ascertain the safety and quality of each batch of cosmetic product and meet required standards. The specific parameters to be tested are selected depending on the product's physical state (gas, liquid, semi solid, or solid) and type of product formulation (e.g., paste, cream, lotion, solution, aerosol, stick). The most commonly investigated parameters are organoleptic properties (color, odor), pH, viscosity, density, partition coefficient, or phase separation [80–82].

Stability tests are conducted to ensure that a cosmetic product meets all the physicochemical and microbiological standards during the intended shelf life when stored in

normal, reasonably foreseeable conditions, and that no changes occur during transport, storage and handling the product [11]. They involve storing the product for a specified time in various conditions of temperature, humidity, mechanical stress, or UV light to verify its stability. Stability tests also allow the determination of the minimum durability of the product and its period after opening or to select appropriate parameters to monitor product changes over time. In addition to the physical stability of cosmetic products, compatibility between a cosmetic product formulation and its final packaging is checked. This is due to possible mutual interactions between the container, its content, and the external environment influencing stability.

Another important element of product safety and quality assurance is microbiological testing that verifies the degree of microbiological purity of cosmetics. It is required by the 1223/2009 Regulation and placed in the Cosmetic Product Safety Report and Product Information File [10]. Microbial specification includes enumeration of bacteria, yeast, and molds, and aims to ensure that the finished product is compliant with the requirements for microbial limits for cosmetics specified in the standard ISO 17516 Cosmetics—Microbiology—Microbiological Limits [83]. An additional legal requirement is to challenge finished cosmetic products with microbial contamination prior to release to market. The challenge test is intended to demonstrate the effectiveness of the preservation system used. It may not be required for low-microbiological-risk and single-use products.

There are no guideline-recommended methods for the assessment of the above-mentioned properties of cosmetic products. It is performed using standard analytical methods as well as specific manufacturer or contract testing laboratory procedures selected depending on the product type and its intended use [83–86].

To comply with legislation [10,12], apart from providing data supporting the safety of the cosmetic product, a manufacturer is also obligated to create and present to competent authorities a Product Information File (PIF) that includes various types of evidential support to substantiate product claims made. The relevant testing strategy and procedures depend on the type of claims (performance, sensorial, ingredients, or perception among other), and may include clinical studies, consumer perception tests, instrumental methods, surveys, and literature reviews [87].

In silico cosmetic-specific approaches to the assessment of a wide range of functional, sensorial, and efficacy-related endpoints are rather scarce, and most of them are very recent. We found only a limited number of models in the available literature (Table 5).

Table 5. Examples of the cosmetic-specific models for functional, sensorial, and efficacy-related endpoints available in the literature.

Endpoint Group	Endpoint	Model Type; Algorithm Used	Input	Author
Physicochemical properties	Stratum corneum partition coefficient	Mechanistic; COSMOmic and Molecular Dynamics	Structure–chemical potential	Piasentin, 2023 [88]
	Spreadability	Empirical	Apparent viscosity, density, melting range	Bom, 2021 [89]
	Spreadability	Empirical; linear regression, non-linear regression based on random forest regressor algorithm	Large amplitude oscillatory shear	Lee, 2022 [90]
	Quality of cream (total number of germs, pH, evaporation residue, relative density, evaporation loss)	Empirical; regression	Total number of germs, pH, evaporation residue, relative density, evaporation loss	Manea, 2023 [91]

Table 5. *Cont.*

Endpoint Group	Endpoint	Model Type; Algorithm Used	Input	Author
Performance	Cleansing capability prediction	Empirical; random forest, extra tree regressors, lasso, partial least squares, support vector regressor	Molecular descriptors and Hansen solubility index	Hamaguchi, 2023 [92]
	Sun Protection Factor, UVA protection, photostability, blue light irradiation protection, free radicals generation	BASF Sunscreen Simulator	Absorption and scattering properties	Osterwalder, 2014 [93]
	Sun Protection Factor, Critical Wavelength, blue light protection factor, Normalized transmitted UV Dose	DSM Sunscreen Optimizer	Type and concentration of UV filters, the emollient system, and the formulation viscosity	https://sunscreensimulator.basf.com/Sunscreen_Simulator/login [accessed on 15 March 2024]
	Fragrance retention grades	Empirical; random forest, support vector machine, and deep neural network	Molecular descriptors (Dragoor)	Liu, 2021 [94]
Sensorial	Overall sensorial rating; formulation optimization	Empirical; Artificial neural network	Physicochemical properties and product specifications	Zhang, 2020 [95]
	Sensory texture properties (Gloss, Integrity of Shape, Penetration Force, Compression Force, Stringiness and Difficulty of Spreading)	Empirical; linear simple, linear multiple and Partial Least Square (PLS) regressions	Instrumental parameters	Gilbert, 2021 [96]
	Optimal fragrance formulation	Empirical; Artificial neural network	Fragrance composition	Santana, 2021 [97]
	Odor perceptual qualities	Empirical; Support Vector Machine	Physicochemical properties (DRAGON)	Kowalewski, 2021 [98]

4. Discussion

As was stated in the introduction, this review did not aim to provide a detailed description of all available computational models developed and utilized for cosmetic development. The aim was to make various parties, potentially interested in applying such methods, aware of the range of available solutions. With that, several areas where mathematical models are in use—skin sensitization prediction as an example—were not thoroughly described, as this would require a separate review paper.

Trying to answer the question stated in the title, we would have to say no, in our opinion, we do not use the opportunity. We, not the royal 'we', but we as a community, underutilize the potential that lies in mathematical models of various types. It is rather peculiar that most of the examples given above come from areas that are strictly required as part of the regulated assessment procedure. As the need creates the solution, having cheaper (well, in general) tools that can replace, at least partially, relatively expensive and time-consuming in vitro experiments resulted in a large number of in silico systems used for chemical safety screening. This remains in agreement with the recently published commentary by Florian Markowetz [99]. Using models from the clinical realm as an example, the author suggests that most of the mathematical models are not only wrong (which we as a community agree with, in general) but also... useless. This utilitarian approach is based on a conclusion that even if the models are formally correct and correctly describe reality, they are not used to help patients. Using this example in cosmetic development, one can see very similar mechanisms, however, from the other end, as models operating in the areas accepted by the regulatory bodies are being predominantly developed. As the regulatory acceptance has been mentioned, it is worth noting that at this stage, in silico models are predominantly used for internal decision making as official regulations are scarce [100]. The detailed discussion of the regulatory drivers of the in silico methods use

in cosmetic substances is out of the scope of this manuscript. Readers interested in more detailed analysis can reach for the work of Taylor and Rego Alvarez [101].

Other potentially useful areas are underrepresented, and by logical cause and effect relationship analogy modeling, the simulation approach is underused. So, what really appears to be a problem is external, formal, or legal acceptance rather than models' quality and their potential usefulness. In our opinion, the area that could benefit from wider expansion of mathematical models is the assessment of skin penetration, systemic exposure assessment, and specifically, formulation optimization. Utilization of mechanistic models allowing for virtual testing of the consequences in terms of local and potentially systemic exposure for various combinations of excipients enables significant scientific gains and financial savings.

To conclude, we believe that the general concept of in silico method utilization, together with validated models and, to some degree, data to parametrize them are already available. What is lacking is an attitude and scientific courage to take this to the next level.

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