Risk Assessment Of Cosmetic Preservatives Using QSAR: QSAR Of Cosmetic Preservatives

Anushka B. , Gadhave Deshmukh ,Komal P. Miskin , Sandhya P. Kadam
Yspm's yashoda technical campus, faculty of pharmacy, wadhe, satara-415015, maharashtra.

Abstract

The evaluation of cosmetic safety for these substances is increasingly encountering scientific and ethical hurdles due to the global limitations on animal testing. Quantitative Structure–Activity Relationship (QSAR) modeling has become a significant computational method for forecasting biological activity and toxicity based on chemical structure. This review combines theoretical principles, methodological progress, and regulatory viewpoints to assess QSAR's role in the risk assessment of cosmetic preservatives. It emphasizes the principles of model development, the necessity for high-quality data, criteria for regulatory acceptance, and integration into contemporary frameworks like the OECD (Q)SAR Toolbox, REACH, and SCCS guidelines. Case studies involving parabens, phenoxyethanol, and organic acids are presented to illustrate practical applications. The review concludes by discussing limitations, ethical considerations, and future directions involving artificial intelligence (AI), multi-omics, and digital-twin integration. Ultimately, QSAR serves as a fundamental component of next-generation, non-animal cosmetic safety assessment, aligning with both sustainability and consumer protection objectives.

Keywords
Cosmetic preservatives; QSAR; in silico toxicology; risk assessment; OECD; SCCS; paraben; phenoxyethanol; ; regulatory science.

Introduction

The global cosmetics industry ranks among the most rapidly expanding areas of applied chemistry, involving products that come into direct contact with human skin, hair, and mucosal surfaces. Ensuring the safety of cosmetic ingredients, especially preservatives, is a crucial goal for both regulatory bodies and public health. Preservatives play a role in preventing microbial growth, thereby extending the shelf life of products and reducing the risk of infections. However, some preservatives have been linked to negative effects such as skin sensitization, endocrine disruption, and environmental harm. Traditionally, the toxicological assessment of these substances has heavily depended on in vivo animal testing. With legislative prohibitions on animal testing, such as the EU Regulation 1223/2009, there is an urgent need for alternative non-animal methods. Among these alternatives, Quantitative Structure–Activity Relationship (QSAR) modeling provides a mechanistic and predictive approach to assess toxic potential based solely on molecular structure. QSAR combines chemistry, toxicology, and computational science to predict activity through statistical or machine-learning algorithms that link molecular descriptors with experimental outcomes. This comprehensive review seeks to bring together current knowledge on QSAR-based methods in cosmetic risk assessment. It discusses conceptual foundations, regulatory acceptance, methodological processes, and the ethical shift towards non-animal strategies. Special focus is given to preservative safety, as these substances illustrate the challenges of balancing effectiveness, safety, and consumer expectations.

Historical Background of QSAR Development

Early Foundations (1960s–1980s) The idea of linking chemical structure to biological activity dates back to the 19th century. However, systematic mathematical formulation began with Hansch and Fujita (1964), who introduced the linear free-energy relationship (LFER) that correlates lipophilicity and electronic properties with pharmacological activity. These initial QSAR models used regression equations with simple physicochemical parameters like partition coefficient (log P), Hammett constant (σ), and molecular refractivity (MR). By the 1970s, QSAR gained traction in pharmaceutical research, leading to significant milestones such as the introduction of Hansch analysis and Free–Wilson models. In environmental toxicology, Verhaar et al. developed structure-based classification schemes for aquatic toxicity, laying the foundation for future ecotoxicological QSARs.

Evolution Toward Multivariate and 3-D Models (1990s–2000s)

Advances in computational power allowed for the development of multidimensional QSAR models that incorporate molecular shape, electrostatic potential, and hydrophobic surface mapping. Techniques like Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Indices Analysis (CoMSIA) emerged, enabling three-dimensional quantitative modeling. Simultaneously, machine-learning algorithms such as k-nearest neighbor (k-NN), partial least squares (PLS), and support vector machines (SVM) expanded QSAR beyond linear relationships. The 1990s also saw the establishment of international initiatives like the OECD QSAR Project, which set best practices for model validation and documentation.

QSAR in Regulatory Toxicology (2000s–Present)

The introduction of REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) in the European Union accelerated QSAR's acceptance in regulatory contexts. REACH permits QSAR predictions as alternative data for chemical registration, provided models adhere to the OECD's five validation principles. Cosmetic regulations adopted similar principles, allowing for non-animal assessment of preservatives. Concurrently, public databases such as ECHA's IUCLID, ECOTOX, and COSMOS have made curated toxicity data available for model training. QSARs are now part of integrated approaches to testing and assessment (IATA), used alongside in vitro and read-across methods.

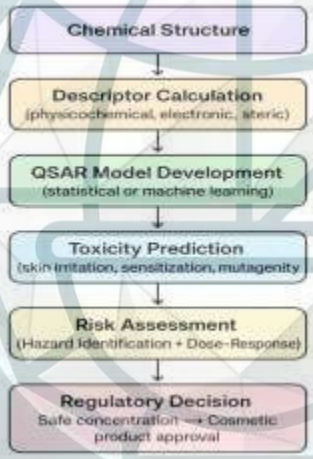
Theoretical Foundation of QSAR Modeling

Fundamental Premises The fundamental tenet of QSAR is that related compounds have similar biological actions. Molecular structure is converted into numerical descriptors using quantitative modelling, which captures steric, electronic, and hydrophobic properties pertinent to activity. A deterministic link between these descriptors and measured biological endpoints is assumed by the procedure.

Molecular Descriptors

Category	Examples	interpretation
Constutional	Molecular weight, atom counts, H-bond donors	Basic composition
Topological	Wiener index, connectivity, kier-Hall indices	Molecular graph relationships
Geometric	Molecular volume,surface area	3-D Conformation
Electronic	Dipole moment,HOMO-LUMO	Electron distribution
Physicochemical	Log P, pKa, solubility	Interaction with biological media

workflow



QSAR

QSAR links a chemical's structure to its impact on living things through the use of mathematical models. To predict toxicity, irritation, allergy potential, or environmental impact, it studies characteristics such as molecule size, structure, and functional groups. Before preservatives and other substances are used in cosmetics, QSAR assists in ensuring their safety. Because it is quick, affordable, and compliant with ethical standards by avoiding animal testing, it is commonly utilised.

Softwares Used

1. OECD QSAR Toolbox: A no-cost resource aiding in chemical hazard evaluation through read-across and trend analysis, ideal for bridging gaps in toxicity data.
2. TOPKAT: A proprietary QSAR platform addressing toxicity endpoints such as mutagenicity, carcinogenicity, and LD50 prediction.

3. MultiCASE: A commercial application extensively utilized for interpreting toxicological data and forecasting toxicity.
4. ADMEWORKS ModelBuilder: Tailored for drug discovery, this tool integrates QSAR with ADMET prediction and can be customized for specific research requirements
5. Schrödinger Suite: An all-encompassing drug discovery suite that facilitates QSAR modeling along with molecular dynamics and protein modeling.
6. LigandScout: Focused on 3D QSAR analyses, it assists in distinguishing between active and inactive molecules.
7. Biovia Materials Studio: Offers simulation tools with a robust QSAR module for predicting material and chemical properties.
8. CarcinoPred-EL: A complimentary online service for predicting carcinogenicity.
9. DeepTox: Software for toxicity prediction utilizing deep learning techniques.
10. Tox-RCNN: A deep learning tool based on CNN for evaluating cell-based cytotoxicity.
11. MuDRA: A Chembench module that employs k-nearest neighbor methods for interpretable QSAR toxicity modeling.
12. OPERA: Created by NIEHS, this tool forecasts toxicity and physicochemical properties, available in both command-line and GUI formats, and integrates with QSAR Toolbox for non-animal hazard assessment.
13. TerraQSAR and MDL QSAR: Additional tools for predicting acute toxicity (LD50) in rodent models.

Cosmetic Preservatives

Cosmetic preservatives are substances added to cosmetic products to prevent the growth of microorganisms, thus prolonging the shelf life and ensuring product safety. They must be effective but safe for human use.

QSAR modeling has been used in the risk assessment and design of cosmetic preservatives to predict toxicities such as skin sensitization, repeated-dose toxicity, and reproductive toxicity. QSAR models can analyze molecular descriptors of preservatives to forecast their biological activity and safety profile, reducing the need for animal testing.

Preservatives studied in QSAR research include parabens, phenoxyethanol, organic acids, and various aliphatic and aromatic compounds. Molecular dynamics simulations coupled with QSAR have been utilized to understand preservative interactions with polymers and predict preservation efficacy as well. This computational approach helps in selecting and designing safe preservatives with optimal performance while minimizing adverse effects, supporting regulatory compliance and consumer safety in the cosmetic industry

Mechanism of Preservatives

The outer membrane of Gram-negative bacteria serves as a selective barrier, safeguarding the bacteria from harmful substances and antibiotics while permitting essential nutrients to pass through. This membrane is

primarily composed of lipopolysaccharides (LPS) on the outer layer and phospholipids on the inner layer. Transport across this intricate structure mainly occurs through three primary pathways:

1. Hydrophilic Pathway –
   This pathway facilitates the entry of polar or water-soluble molecules into the bacterial cell through protein channels called porins. These porins create aqueous pores that span the outer membrane, allowing molecules to passively diffuse based on their size and charge. Mechanism: • Porins like OmpF, OmpC (in E. coli), and OprD (in Pseudomonas aeruginosa) form trimeric β-barrel structures. • Each monomer has a channel filled with water and lined with polar residues. • Small hydrophilic molecules move down their concentration gradient through these channels. • Selectivity is determined by: • Size exclusion limit (typically < 600 Da) • Charge filtering, as many porins have negatively charged interiors • Hydrophilicity of the molecule Examples: • β-lactam antibiotics (e.g., ampicillin, cephalosporins) • Small sugars (glucose, maltose) • Ions and amino acids Significance: • Porins are crucial for antibiotic uptake; thus, mutations or loss of porins can lead to antibiotic resistance. • In Pseudomonas, reduced expression of OprD results in resistance to carbapenems. • QSAR models often examine how molecular size and polarity affect porin-mediated transport efficiency.

   2. Hydrophobic Pathway – Diffusion through the Lipid Bilayer .
   This pathway allows nonpolar, lipophilic molecules to traverse the hydrophobic core of the outer membrane lipid bilayer. Mechanism: • Although the outer membrane contains hydrophilic LPS molecules on its surface, it also has hydrophobic lipid tails that form a barrier. • Lipophilic molecules can integrate into this lipid region, diffuse through it, and then enter the periplasmic space. • The diffusion rate depends on: • Lipid solubility (log P value) • Molecular size and shape • Membrane fluidity and temperature Examples: • Chloramphenicol (a moderately lipophilic antibiotic) • Rifampicin (for Mycobacterium tuberculosis) • Some dyes and small hydrophobic drugs

Significance: • This route is limited in Gram-negative bacteria because the LPS layer is highly polar, impeding the entry of lipophilic compounds. • However, Gram-positive bacteria (which lack an outer LPS membrane) rely more on this pathway. • In QSAR studies, lipophilicity (often measured as logP) is a key descriptor for modeling hydrophobic diffusion efficiency. 3. Self-Promoting Uptake Pathway – Membrane Destabilization Mechanism Overview: This unique pathway is primarily used by cationic antimicrobial peptides (CAMPs) and some antibiotics like polymyxins. Instead of passive diffusion, these molecules actively disrupt the bacterial outer membrane by interacting with LPS molecules.

Mechanism:

•The stability of the outer membrane in Gram-negative bacteria is maintained by divalent cations like Mg^{2+} and Ca^{2+}, which form bridges between negatively charged LPS molecules. •Cationic antibiotics, which carry a positive charge, compete for these binding sites, displacing the divalent cations. •This displacement causes the LPS layer to become unstable, resulting in localized disruption of the outer membrane. •Once the membrane is disrupted, the drug can penetrate the phospholipid bilayer, increasing permeability and leading to cell lysis or facilitating the entry of other drugs. Examples: •Polymyxin B •Colistin (Polymyxin E) •Certain synthetic cationic peptides

Significance: •This mechanism is often bactericidal, not merely a transport pathway. •It serves as the foundation for combination therapies, where polymyxins enhance membrane permeability to other antibiotics.

•However, excessive use can result in membrane toxicity in humans and the development of resistant strains, such as those mediated by the mcr-1 gene. •QSAR models analyzing this mechanism often consider factors like electrostatic charge distribution, cationic density, and the hydrophobic balance of the molecule.

Microbial Safety In Cosmetics

The microbiological safety of cosmetics is evaluated through antimicrobial preservation efficacy tests based on standards like the US Pharmacopoeia and EU Pharmacopoeia, which are primarily designed for pharmaceuticals under stringent GMP conditions. However, these pharmacopoeial tests typically focus only on pathogenic microorganisms. In contrast, the schülkeKoKo test is specifically developed for cosmetics, covering both pathogenic and product-spoiling microorganisms based on extensive industry experience. This mixed-germ spectrum approach better simulates real-world microbial environments and allows for symbiotic microbial growth, providing a more realistic assessment of preservative effectiveness. It uses agar media to simultaneously detect bacteria and fungi, ensuring that microbial growth indicates insufficient preservation, thus avoiding misinterpretation caused by microbial competition. Additionally, to mimic actual production and usage scenarios, multiple inoculations are performed. Hence, the schülkeKoKo test offers a reliable evaluation of cosmetic preservative efficacy. Preservatives, due to their low molecular weight, can cause intolerance reactions, posing safety concerns alongside efficacy challenges. Therefore, the cosmetic industry emphasizes both preservative effectiveness and consumer safety. Apart from antimicrobial agents, other preservation strategies include controlling water activity, adjusting pH, and using multifunctional ingredients to enhance product stability and safety.

Water Activity

Water activity (aw) is distinct from the total water content in a product. It quantifies the amount of unbound water, which is not chemically attached to other components in the product. As per Raoult's law, water activity is described as the ratio of the product's water vapor pressure (P) to the vapor pressure of pure water (P_0) at the same temperature. In this scenario, n_1 denotes the moles of solvent, and n_2 signifies the moles of water

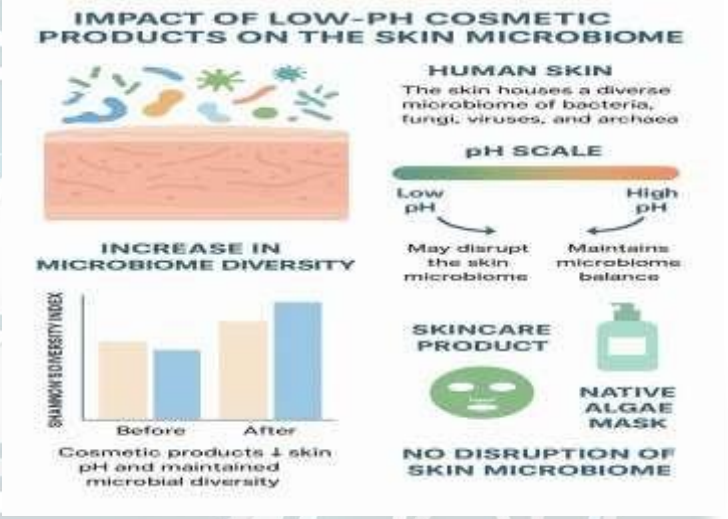
$$. a_w = X_w Y_w$$

Here, n_w stands for the moles of water, n for the moles of solute, X_w is the mole fraction of water, and Y_w is the activity coefficient of water. Water activity is also linked to osmotic pressure through the equation

$$: \Pi = -RT \ln(a_w)$$

where R is the gas constant, T is the absolute temperature, and \ln(a_w) is the natural logarithm of water activity. Numerically, water activity is equivalent to one-hundredth of the relative humidity (RH) that the product generates in a sealed environment. This indicates it measures the free or available moisture in the material. It can be determined by directly measuring partial vapor pressure, dew point, or using sensors that assess relative humidity. Measurement of water activity (aw) Assessing water activity in cosmetic products is crucial for evaluating key attributes like microbial safety and chemical stability, including the stability of fats, degradation of vitamins and proteins, and enzyme activity. It also influences physical properties such as color, texture, and mechanical behavior. This discussion emphasizes using water activity measurements to evaluate microbial stability. There are several methods to measure water activity, with hygrometric techniques being the most prevalent.

Ph Control



The human skin acts as a shield against external pathogens and hosts a diverse microbiome consisting of bacteria, fungi, viruses, and archaea. Any disturbance to this microbiome can impact immune function, potentially resulting in inflammatory and autoimmune conditions. Maintaining an appropriate pH level is essential for microbiome balance. Cosmetic skincare products affect both skin pH and the microbiome, playing a crucial role in maintaining microbial balance. Research suggests that products with non-physiological pH levels may disrupt the skin's microbial community. Our clinical study assessed the effects of low-pH cosmetic products (pH below 5) on the skin microbiome over a 28-day period. We examined four products—vitamin C concentrate, resveratrol concentrate, a collagen mask, and a native algae mask—applied to the forearms of post-menopausal women with skin pH above 5.5. Throughout the study, skin microbiome diversity consistently increased in both untreated areas and after product application, as indicated by Shannon's diversity index. The native algae mask significantly reduced the abundance of Corynebacterium bacteria and notably lowered skin pH. Changes in skin pH were linked to microbiome stability. In conclusion, the diversity of the natural skin microbiome improved during the study, and none of the tested products caused significant disruption in microbial diversity, as evidenced by stable Shannon's diversity index values and consistent levels of key bacterial groups. Notably, the native algae mask decreased the opportunistic pathogenic Corynebacterium, likely due to its slight pH-lowering effect with prolonged use. These findings suggest that low-pH skincare products, such as the native algae mask, do not harm skin microbiome diversity and may enhance skin health by reducing certain pathogenic microbes. The clinical study focused on evaluating the skin microbiome diversity following the application for 28 days of four different low-pH cosmetic products (vitamin C, resveratrol, a collagen mask, and a native algae mask) on the forearms of post-menopausal women with skin pH > 5.5. Results: The diversity of the natural skin microbiome increased consistently throughout the study, evident in both the untreated area and after the application of the Vitamin C Concentrate, Resveratrol Concentrate, Collagen Mask, and

Native Algae Mask, as indicated by Shannon's diversity index. The native algae mask notably reduced the Corynebacterium genus and significantly lowered the pH. The skin pH changes corresponded with microbiota stability.

Challenge Test in cosmetics

Definition

A microbiological test called the Challenge Test (also known as the Preservative Efficacy Test or Antimicrobial Effectiveness Test) is used to assess how well a preservative system works in cosmetic products. It guarantees that even after being exposed to possible contamination during routine consumer usage, the product will remain microbiologically safe and stable for the duration of its shelf life.

Purpose

To confirm the cosmetic product's ability to withstand microbiological contamination.
To guarantee the stability and safety of the product.

To comply to global regulations
Determine the necessity of reformulation or more potent preservatives.

Microorganisms Commonly Used

Standard challenge tests use specific reference strains that represent the main types of potential contaminants:

Type	Test Organism	Strain Example
Gram-positive bacterium	Staphylococcus aureus	ATCC 538
Gram-negative bacterium	Pseudomonas aeruginosa	ATCC 9027
Gram-negative bacterium	Escherichia coli	ATCC 8739
Yeast	Candida albicans	ATCC 10231
Mold (fungus)	Aspergillus brasiliensis	ATCC 16404

Microorganisms Process (Step-by-Step)

Step These species were picked because they are typical spoilage and pathogenic
1. Sample Preparation: • The cosmetic product (gel, lotion, cream, etc.) is made aseptically. • Preservatives must be included in the product's complete formulation.
Step
2. Inoculation • Each microorganism is given to distinct product samples at a predetermined concentration (10◦–10◦ CFU/g or mL). • To guarantee uniform dispersion, every sample is carefully mixed.

Step 3: Incubation • The infected items are kept at a temperature of 20 to 25 degrees Celsius with regulated humidity.

Step 4: Counting Microorganisms Samples are collected at predetermined intervals, usually on Days 0, 7, 14, and 28. Using plate count techniques, the quantity of viable bacteria (CFU) is determined at each interval.
Step 5: Evaluation • The reduction in viable microorganisms is compared to the original inoculum. • The preservative system can be considered effective if microbial growth is either absent or significantly reduced over time.

Evaluation Criteria (ISO 11930:2019 Standard)

The product passes if microbial counts meet specific reduction thresholds over time

Microorganism	7 Days	14 Days	28 Days
Bacteria	≥ 3 $\log_{10}$ reduction	No increase	No increase
Yeast & Mold	≥ 1 $\log_{10}$ reduction	No increase	No increase

"Log reduction" means a 10-fold reduction in microbial numbers. For example, a 3 log reduction = 99.9% decrease in viable bacteria.

Interpretation of Results

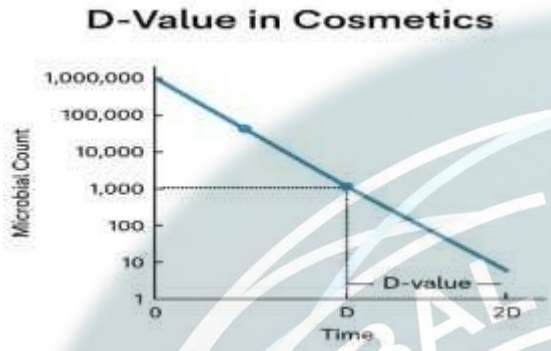
Result	Interpretation
Microbial count drops rapidly and remains low	Preservative system is effective
Microbial count decreases slowly or regrows	Preservative system is marginal
No reduction or increase in microbes	Preservative system fails

D Value
An essential microbiological metric used to gauge an organism's resistance to a particular sterilisation or preservation procedure, such as heat, radiation, or chemical preservatives, is the D-value (Decimal Reduction Value). It is frequently used in food microbiology, cosmetics, and pharmaceuticals to assess the efficacy of preservatives and germ killing.
D-value is the amount of time required to eradicate 90% of the microorganisms under specific conditions or at a constant temperature.

Application of D-Value in Cosmetics
In cosmetic microbiology, the D-value helps evaluate:

1. Preservative Efficacy: The rate at which preservatives lower the microbiological burden in challenge testing.

2. Product Sterilisation: Calculating the temperature and duration required to render microorganisms inactive during manufacturing
3. Shelf-Life Prediction: Calculating the stability of microorganisms during storage.
4. Heat or Chemical Resistance Comparison: Evaluating how resistant certain microorganisms are to thermal processing or preservatives.



COSMETIC REGULATIONS/LEGISLATION

Cosmetic regulations play a crucial role in ensuring that products available in the market are safe for human use, properly labeled, and free from harmful substances. Although the specific requirements vary by country and region, the overarching aim is to safeguard consumer health and maintain trust in cosmetic products. Worldwide, regulatory bodies oversee the formulation, testing, labeling, and marketing of cosmetics, with a particular focus on assessing the safety of individual ingredients like preservatives.

Definition of Cosmetics According to the European Commission (EC Regulation No. 1223/2009), cosmetics are defined as any substance or mixture intended for application to the external parts of the human body, primarily for cleaning, perfuming, altering appearance, protecting, maintaining condition, or correcting body odors. Similarly, the U.S. Food and Drug Administration (FDA), under Section 201(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), defines cosmetics as articles intended for application to the human body for cleansing, beautifying, enhancing attractiveness, or altering appearance.

Key Global Regulatory Frameworks

1. European Union (EU) • Regulation (EC) No. 1223/2009 is the primary legislation governing cosmetics in the EU. • Key Features: • Prohibits animal testing for cosmetics and cosmetic ingredients. • Requires a safety assessment by a qualified professional (toxicologist or chemist). • Mandates a Product Information File (PIF) including toxicological data and safety evaluation. • Establishes a Cosmetic Product Notification Portal (CPNP) for product registration. • Includes Annexes listing prohibited substances, restricted substances, colorants, preservatives, and UV filters.

2. United States (FDA) • Regulated under the FD&C Act and Fair Packaging and Labeling Act (FPLA). • Key Features: • No pre-market approval is required for most cosmetics (except color additives). • The manufacturer is responsible for product safety before marketing. • The FDA enforces labeling, adulteration, and misbranding rules. • In 2022, the Modernization of Cosmetics Regulation Act (MoCRA) was

introduced to strengthen oversight—requiring product listing, safety substantiation, and adverse event reporting.

3. India • Governed by the Drugs and Cosmetics Act, 1940 and the Cosmetics Rules, 2020. • Key Features: • Overseen by the Central Drugs Standard Control Organization (CDSCO). • Manufacturers must obtain a manufacturing license. • Bans the import of cosmetics tested on animals. • Requires labeling, ingredient disclosure, and safety evaluation. • Sets limits on heavy metals and other contaminants.

4. Japan • Regulated by the Pharmaceutical and Medical Device Act (PMD Act). • Key Features: • Cosmetics are classified as either quasi-drugs or ordinary cosmetics. • Quasi-drugs require pre-market approval for ingredients and efficacy claims. • The Ministry of Health, Labour and Welfare (MHLW) oversees approval and compliance.

5. China • Regulated by the Cosmetic Supervision and Administration Regulation (CSAR), effective 2021. • Key Features: • Differentiates between special cosmetics (e.g., hair dye, sunscreen) and general cosmetics. • Requires safety assessments and ingredient registration. • Introduced exemptions for animal testing under specific conditions. • Overseen by the National Medical Products Administration (NMPA)

6. Other Areas
• Canada: Under Health Canada's Cosmetic Regulations and the Food and Drugs Act. • Australia: governed by the Therapeutic Goods Administration (TGA) and the Industrial Chemicals Environmental Management (Register) Act 2021. •ASEAN: To promote commerce while maintaining safety, member nations' regulations are harmonised through the ASEAN Cosmetic Directive (ACD).

ENVIRONMENTAL AND HEALTH IMPACT OF PRESERVATIVES

Preservatives are crucial elements in cosmetic products, serving an essential function in preventing microbial growth and maintaining the chemical and physical stability of these products throughout their shelf life. Cosmetics that include water or nutrient-rich bases create an ideal environment for microorganisms like bacteria, fungi, and yeast to thrive. Without proper preservation systems, microbial contamination can undermine the stability and appearance of these formulations, leading to spoilage and potentially causing health risks to consumers, such as skin infections or allergic reactions. Therefore, the inclusion of effective preservatives is vital to ensure the safety, quality, and durability of cosmetic products during storage and use. Despite the heavy dependence on synthetic preservatives, there are growing concerns about their impact on the environment and human health. The frequent use of cosmetics results in ongoing and cumulative exposure to these chemicals. After application, a significant portion of cosmetic residues is rinsed off and enters wastewater systems. Due to their chemical stability and fat-loving nature, many preservatives are resistant to biodegradation and remain in aquatic environments, where they can build up in sediments and organisms. Consequently, certain preservatives, like parabens and triclosan, are increasingly identified as new environmental pollutants. Research shows that these substances can have ecotoxicological effects, such as disrupting aquatic reproduction, altering microbial communities, and accumulating through food chains. These findings highlight the need for sustainable management and strict regulatory control over preservative use. At the same time, the toxicological effects on human health are still being actively studied. Long-term skin exposure, especially from leave-on cosmetics, can cause irritation, sensitization, or allergic dermatitis. Compounds like isothiazolinones and formaldehyde-releasing

agents are known sensitizers, while parabens and phenolic preservatives have shown weak endocrine-disrupting effects by binding to estrogen receptors. Although regulatory agencies generally limit their concentrations to safe levels, there are ongoing concerns about chronic low-dose exposure and potential interactions among various cosmetic ingredients. Additionally, preservatives with strong antimicrobial properties can disrupt the natural skin microbiome, weakening the skin's defenses and leading to inflammation and barrier issues.

HAZARDOUS INGREDIENTS IN COSMETICS

Cosmetic products are now a staple in daily life, serving aesthetic, hygienic, psychological, and social functions. These products are made up of complex mixtures of chemical and natural ingredients, including emulsifiers, surfactants, colorants, fragrances, UV filters, and preservatives, each contributing to the product's stability, appearance, and sensory qualities. However, increasing scientific evidence has raised concerns about the safety of certain cosmetic ingredients that may pose risks to human health and the environment if used improperly or over long periods. Preservatives are one of the most crucial components in cosmetic formulations, playing a key role in preventing microbial contamination and ensuring product stability throughout its shelf life. Cosmetics, especially those with water or nutrient-rich bases, provide ideal conditions for the growth of microorganisms like bacteria, fungi, and yeast. Without effective preservation systems, microbial contamination can compromise product quality and safety, leading to spoilage and health risks such as skin infections or allergic reactions. Therefore, the inclusion of appropriate preservatives is essential for maintaining both the microbiological safety and physicochemical stability of cosmetic products during production, storage, and use. Although synthetic preservatives and other cosmetic additives play a crucial role, they have been under scrutiny for their potential toxicological and environmental effects. The frequent and prolonged use of cosmetics results in continuous, low-level exposure to various chemical substances, some of which have properties that can disrupt endocrine function, cause allergies, or even lead to cancer. Once used, these chemicals often make their way into wastewater systems, where they resist breaking down and remain in aquatic environments. Substances like parabens, triclosan, and UV filters based on benzophenone are identified as emerging environmental pollutants, showing potential for bioaccumulation, ecotoxicity, and interference with aquatic reproductive systems. This persistence has sparked global concerns about long-term environmental safety and the need for regulatory oversight.

Categories of Hazardous Cosmetic Ingredients

Preservatives

Preservatives are used to prevent microbial contamination, but improper use can lead to toxic, allergenic, or endocrine-disrupting effects. •Parabens (methyl-, ethyl-, propyl-, butylparaben): These are known for their potential estrogen-like activity, reproductive toxicity, and possible disruption of endocrine functions. •Formaldehyde-releasing agents (e.g., imidazolidinyl urea, DMDM hydantoin, quaternium-15): These can cause skin sensitization and allergic reactions. •Isothiazolinones (MI, MCI): These are strong sensitizers associated with widespread contact dermatitis cases. •Triclosan and triclocarban: Once popular as

antimicrobial agents, they are now restricted due to concerns about bioaccumulation, thyroid hormone disruption, and antimicrobial resistance.

Fragrances and Musks

Fragrance mixtures consist of numerous volatile organic compounds, some of which are linked to allergic reactions, respiratory irritation, and phototoxicity. •Synthetic musks (musk xylene, musk ketone) persist in the environment and accumulate in human tissues. •Limonene and linalool, when oxidized, can act as skin sensitizers. •Certain phthalates (e.g., diethyl phthalate, DEP) used as fragrance carriers are suspected endocrine disruptors and have been linked to reproductive toxicity.

Colorants

Color additives enhance the visual appeal of cosmetics but may contain toxic heavy metals or aromatic amines as contaminants or degradation products. •Coal tar dyes and azo colorants may release carcinogenic aromatic amines upon metabolic breakdown. •Heavy metal impurities (lead, arsenic, cadmium, mercury) have been detected in lipsticks, eye shadows, and skin-lightening creams, causing neurological, renal, and developmental toxicity. •Despite regulatory limits, contamination from pigments or raw materials remains a concern, particularly in unregulated or counterfeit products.

Ultraviolet (UV) Filters

UV filters protect the skin from photoaging and UV-induced damage but may act as endocrine disruptors and environmental pollutants. •Oxybenzone (benzophenone-3) and octinoxate (ethylhexyl methoxycinnamate) have been shown to mimic estrogen and disrupt thyroid function. •These compounds persist in aquatic environments and have been implicated in coral reef bleaching and aquatic toxicity.
•Safer alternatives, such as zinc oxide and titanium dioxide nanoparticles, are being adopted, though concerns remain regarding nanoparticle inhalation and dermal penetration.

Surfactants and Emulsifiers

Surfactants provide cleansing and foaming properties but can irritate the skin and mucous membranes.
•Sodium lauryl sulfate (SLS) and sodium laureth sulfate (SLES) are associated with skin irritation and barrier disruption, especially with repeated use. •Cocamide DEA and MEA, used as foaming agents, have shown carcinogenic potential in long-term studies due to nitrosamine formation under certain conditions.

Skin-Lightening Agents

Compounds used for depigmentation often include toxic or illegal substances. •Hydroquinone, once widely used, can cause exogenous ochronosis, cytotoxicity, and DNA damage. •Mercury compounds (e.g., mercuric chloride) found in some unregulated creams are neurotoxic and nephrotoxic, leading to severe systemic effects. •The World Health Organization (WHO) and Minamata Convention have called for the elimination of mercury in cosmetics globally.

Health Effects of Hazardous Cosmetic Ingredients

The health impacts of hazardous ingredients vary according to exposure duration, concentration, and route of entry (dermal, inhalation, or oral).

Preservative detected	Products
1. 2-phenoxyethanol	Aftershave balms
2. 4-hydroxybenzoic acid	Anti-stretch marks cream
3. Benzalkonium chloride	Bath gel
4. Benzisothiazolinone	Body care product
5. Benzoic acid	Body milk
6. Benzyl alcohol	Cosmetics
7. Benzylparaben	Creams
8. Bronopol	Deodorant
9. Butylatedhydroxyanisole	Eye drop
10. Butylatedhydroxytoluene	Face cream
11. Butylparaben	Hair conditioners
12. Cetrimonium chloride	Hand creams / gel
13. Chlorhexidinedigluconate	Hand soaps
14. Chlorhexidinedihydrochloride	Hygiene wash
15. Chloroacetamide	Lanoline cream
16. Chlorphenesin	Lipsticks
17. Dehydroacetic acid	Liquid formulations
18. Dimethylol dimethyl hydantoin	Liquid soaps
19. Ethyl benzoate	Lotions
20. Ethylparaben	Makeup
21. Formaldehyde	Moisturizing creams
22. Formalin	Multi-purpose cleaners
23. Formic acid	Oil-based lotions

•Systemic effects: endocrine disruption, reproductive toxicity, neurotoxicity, carcinogenicity. •Cumulative exposure: regular use of multiple products may result in additive or synergistic toxicity. •Certain compounds cross the skin barrier or are absorbed systemically, leading to long-term accumulation in tissues and potential chronic health effects

Environmental Implications: Persistent, bioaccumulative, and toxic (PBT) chemicals include a number of dangerous cosmetic compounds.
Surface waters, sediments, and wastewater effluents frequently contain fragrances, UV filters, and preservatives.
These substances have the potential to bioaccumulate in fish and other species, alter microbial biodiversity, and disturb aquatic ecosystems.

Due of their tendency to bleach coral, sunscreen ingredients like oxybenzone and octocrylene have been outlawed in a number of coastal areas.

Environmental pollution is made worse by the inclusion of non-biodegradable polymers and microplastics in cosmetic formulas.

SAFETY ASSESSMENT OF INGREDIENT IN COSMET

The evaluation of cosmetic ingredients for safety is essential to ensure that products used on human skin, hair, or mucous membranes are safe for their intended application under normal and expected conditions. Given that cosmetics are applied directly to the body and often used over extended periods, it is crucial to thoroughly assess their ingredients for any potential toxicological, dermatological, and systemic impacts. The primary aim of safety assessment is to identify possible hazards, estimate exposure levels, and determine if the margin of safety (MoS) is adequate for human use. Safety evaluation encompasses a combination of toxicological testing, exposure analysis, risk characterization, and regulatory review, all of which collectively form the basis for consumer protection and product safety assurance. The general principle of cosmetic safety assessment follows the risk assessment paradigm, which includes four key steps:

1. Hazard Identification: Identifying the inherent toxicological properties of an ingredient using available experimental data, literature, or predictive modeling. This involves assessing potential skin irritation, sensitization, mutagenicity, carcinogenicity, reproductive toxicity, and systemic effects.

2. Dose–Response Assessment: Establishing the relationship between the level of exposure and the likelihood or severity of an adverse effect. Toxicological studies, such as the No Observed Adverse Effect Level (NOAEL), serve as reference points.

3. Exposure Assessment: Estimating the extent, frequency, and duration of consumer exposure under realistic usage conditions. This takes into account factors such as product type, ingredient concentration, application area, and dermal absorption rate.

(MoS: Margin of Safety)

The Margin of Safety (MoS) is a crucial parameter in cosmetic risk assessment, representing the ratio between the No Observed Adverse Effect Level (NOAEL) and the Systemic Exposure Dose (SED).

Systemic Exposure
The Systemic Exposure Dose estimates the amount of a cosmetic ingredient absorbed per kilogram of body weight per day.

Dermal Absorbed Dose (DAD)
The Dermal Absorbed Dose estimates the total mass of an ingredient that penetrates through the skin.

Acceptable Daily Intake (ADI)
The Acceptable Daily Intake (ADI) defines the amount of a chemical that can be ingested daily over a lifetime without significant health risk.

Bioconcentration Factor (BCF)
For evaluating environmental accumulation, particularly for preservatives and UV filters.

COMPUTATIONAL/QSAR STUDIES

Computational toxicology has emerged as a powerful discipline in modern cosmetic science, offering innovative methods for predicting the biological and environmental behavior of chemical ingredients. Among these techniques, Quantitative Structure–Activity Relationship (QSAR) modeling stands out as a cornerstone approach for assessing chemical safety, particularly in the context of cosmetics where ethical, regulatory, and practical considerations limit the use of animal testing. QSAR models establish statistical correlations between the molecular structure of a compound and its biological activity or toxicological endpoint, thereby enabling the prediction of adverse effects solely from chemical information.

Principle Of Qsar Modeling

The foundation of QSAR (Quantitative Structure–Activity Relationship) modelling is the idea that compounds with comparable structures typically exhibit comparable biological effects. By examining a material's molecular structure, size, shape, and chemical groups, QSAR assists in predicting how safe or hazardous a substance may be in the risk assessment of cosmetics and preservatives. The model estimates potential risks such skin irritation, allergies, toxicity, and environmental damage using computer tools and databases of known compounds. QSAR is a quick, economical, and moral approach since it doesn't include animal testing. It assists scientists in determining acceptable concentration limits, identifying potentially hazardous compounds early, and ensuring that cosmetics fulfil safety regulations prior to being sold to consumers. To put it simply, QSAR predicts a chemical's behaviour and safety based on its structure making cosmetic products safer and more reliable.

Application Ingredient Safety Applications in Cosmetic

QSAR models are increasingly employed to forecast toxicological endpoints pertinent to cosmetic ingredients, such as: •The potential for skin sensitization and irritation, especially concerning preservatives like isothiazolinones and parabens; •Mutagenicity and carcinogenicity, to pinpoint compounds with possible genotoxic risks; •Endocrine-disrupting potential, notably for phenolic and phthalate-based substances; •Environmental fate and bioaccumulation, evaluating persistence and ecotoxicity in aquatic environments. For example, QSAR research on parabens has identified links between alkyl chain length and estrogenic activity, enabling predictions of endocrine disruption risk. Similarly, computational models for methylisothiazolinone (MIT) and benzisothiazolinone (BIT) have been instrumental in predicting skin sensitization potency, aiding regulatory assessments.

Benefits of QSAR in Cosmetic Risk Assessment

The application of QSAR modeling in cosmetic safety evaluation offers several benefits: 1. Ethical compliance: It supports the 3Rs principles (Replacement, Reduction, Refinement) by minimizing the need for animal testing, in line with regulatory bans in the EU and other regions.

2. Cost- and time-efficiency: It facilitates rapid screening of extensive chemical libraries and prioritization of safer alternatives before experimental validation.

3. Mechanistic insight: It provides an understanding of the molecular mechanisms underlying toxicity, aiding in the rational design of ingredients.

4. Regulatory acceptance: Recognized by entities such as the OECD (Organization for Economic Co-operation and Development), ECHA (European Chemicals Agency), and U.S. EPA, with validated QSAR models accepted in regulatory submissions.

Integration with Regulatory and Experimental Data

QSAR models are most effective when combined with other computational and experimental methods, such as read-across approaches, molecular docking, and in vitro assays. Hybrid approaches—merging QSAR predictions with data from cell-based toxicity tests or physicochemical analyses—result in more robust and comprehensive risk assessments. Additionally, databases like COSMOS, VEGA, OECD QSAR Toolbox, and ToxCast offer curated data sets and validated models for evaluating cosmetic ingredients.

Regulatory frameworks, including the EU Cosmetic Regulation (EC No. 1223/2009) and the U.S. MoCRA (Modernization of Cosmetics Regulation Act, v2022), increasingly promote the use of non-animal testing methods, where QSAR-based assessments play a crucial role. These models are particularly useful for assessing newly synthesized preservatives and fragrance compounds with limited empirical toxicity data

Limitations and Future Directions

Despite their advantages, QSAR models have limitations. The accuracy of predictions relies on the quality of input data and the model's applicability domain. Compounds with complex structures, mixtures, or unknown degradation products may not fit well within established models. Additionally, environmental transformations (e.g., photolysis, hydrolysis, microbial degradation) can alter chemical structures, complicating the prediction of real-world behavior.

Future directions in computational toxicology focus on integrating AI and deep learning techniques to enhance model prediction accuracy and interpretability. Combining QSAR with omics-based and systems biology data can further improve the understanding of toxicity mechanisms. The development of machine learning-assisted QSAR (ML-QSAR) and 3D-QSAR methods enables more refined modeling of molecular interactions relevant to cosmetic ingredient toxicity.

Conclusion

Computational and QSAR-based research signifies a transformative approach in evaluating the safety of cosmetics. By forecasting biological and environmental interactions from molecular structures, QSAR offers a scientifically robust, ethical, and efficient method for assessing cosmetic ingredients. When combined with experimental validation and regulatory guidelines, these methods support the creation of safer, environmentally friendly, and sustainable cosmetic products. As technology progresses, the collaboration between computational modeling and empirical data will continue to enhance risk assessment methods and bolster consumer safety assurance throughout the cosmetic industry.

References

1. SCCS (Scientific Committee on Consumer Safety). (2021). The SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation (11th revision). European Commission.

2. OECD. (2014). Guidance Document on the Validation of (Q)SAR Models. OECD Series on Testing and Assessment No. 69.

3. REACH. (2020). Guidance on Information Requirements and Chemical Safety Assessment. European Chemicals Agency (ECHA).

4. Patlewicz, G., & Worth, A. (2020). Review of computational methods for cosmetics safety assessment. Computational Toxicology, 13, 100119.

5. Laws, M., et al. (2023). Non-animal approaches in cosmetic ingredient risk assessment. Regulatory Toxicology & Pharmacology, 137, 105320.

6. Hansch, C., & Fujita, T. (1964). ρ–σ–π analysis: A method for the correlation of biological activity with chemical structure. Journal of the American Chemical Society, 86(8), 1616–1626.

7. Free, S. M., & Wilson, J. W. (1964). A mathematical contribution to structure–activity studies. Journal of Medicinal Chemistry, 7(4), 395–399.

8. Verhaar, H. J. M., et al. (1992). Classifying environmental pollutants: QSAR screening for aquatic toxicity. Chemosphere, 25(4), 573–578.

9. Kubinyi, H. (1997). QSAR and 3D-QSAR in drug design. Drug Discovery Today, 2(12), 457–467.

10. Cherkasov, A., et al. (2014). QSAR modeling: Where have you been? Where are you going? Journal of Medicinal Chemistry, 57(12), 4977–5010.

11. Todeschini, R., & Consonni, V. (2008). Handbook of Molecular Descriptors. Wiley-VCH.

12. Roy, K., et al. (2015). A Primer on QSAR/QSPR Modeling. Springer.

13. Gupta, S. (2011). QSAR modelling principles and applications. Indian Journal of Pharmaceutical Sciences, 73(4), 279–287.

14. Tropsha, A. (2010). Best practices for QSAR model development, validation, and exploitation. Molecular Informatics, 29, 476–488.

15. Cherkasov, A., et al. (2014). QSAR review. Journal of Medicinal Chemistry.

16. OECD. (2023). QSAR Toolbox (v4.6): User Manual.

17. Benigni, R., et al. (2008). In silico predictive models for carcinogenicity. Mutagenesis, 23(4), 277–286.

18. Lagunin, A., et al. (2018). DeepTox: Deep learning for toxicity prediction. Frontiers in Environmental Science.

19. Mansouri, K., et al. (2021). OPERA: Chemical property prediction model suite. NTP/NIEHS.

20. MultiCASE Inc. (2019). CASE Ultra Reference Manual.

21. Halla, N., et al. (2018). Cosmetic preservative systems: Regulatory overview and preservative efficacy testing. Cosmetics, 5, 3.

22. Ates, G., et al. (2020). QSAR models for predicting preservative toxicity. Toxicology in Vitro, 65, 104790.

23. Routledge, E. J., et al. (1998). Estrogenic activity of parabens. Toxicology and Applied Pharmacology, 153(1), 12–19.

24. Andersen, F. A. (2008). Final report on the safety assessment of phenoxyethanol. International Journal of Toxicology.

25. Soni, M. G., et al. (2005). Safety assessment of parabens. Food and Chemical Toxicology, 43(7), 985–1015.

26. ISO. (2019). ISO 11930: Microbiology—Evaluation of the antimicrobial protection of a cosmetic product.

27. USP. (2023). USP <51>: Antimicrobial Effectiveness Testing.

28. Schülke & Mayr. (2010). KoKo Test—Preservative efficacy testing for cosmetics.

29. Russell, A. D. (2003). Microbial resistance and preservative efficacy. Journal of Applied Microbiology.

30. Peleg, M. (2020). D-values and thermal inactivation kinetics. Food Engineering Reviews.

31. Labuza, T. P. (1970). Water activity and food stability. Food Technology.

32. Rahman, M. S. (2009). Food Stability and Water Activity. Springer.

33. Ali, A., et al. (2022). Impact of cosmetic products on skin microbiome and pH. Scientific Reports, 12, 14582.

34. Knor, T., et al. (2023). Skin microbiome responses to low-pH cosmetic formulations. Journal of Cosmetic Dermatology.

35. O'Neill, C. A., et al. (2020). Skin microbiota and barrier function. Experimental Dermatology.

36. European Commission. (2009). Regulation (EC) No 1223/2009 on cosmetic products.

37. FDA. (2022). Modernization of Cosmetics Regulation Act (MoCRA).

38. CDSCO. (2020). Cosmetics Rules. Government of India.

39. NMPA. (2021). Cosmetic Supervision and Administration Regulation (CSAR). China.

40. ASEAN. (2016). ASEAN Cosmetic Directive (ACD).

41. Dhillon, G. S., et al. (2015). Triclosan: Environmental risk review. Environmental Science and Pollution Research.

42. Gao, Y., et al. (2020). Bioaccumulation of UV filters in aquatic environments. Chemosphere.

43. Rastogi, S. C. (2002). Content of preservatives in cosmetics. Contact Dermatitis.

44. Heidorn, C., et al. (2021). Preservatives and human dermal toxicity. Cosmetics, 8(2), 54.

45. Dodson, R. E., et al. (2015). Endocrine-disrupting chemicals in cosmetics. Environmental Health Perspectives.

46. Hamann, C. R., et al. (2014). Isothiazolinone allergy outbreak in cosmetics. Journal of Allergy & Clinical Immunology.

47. Guo, Y., & Kannan, K. (2013). Phthalates and parabens in personal care products. Environmental Science & Technology.

48. Matta, M. K., et al. (2019). Systemic absorption of sunscreens. JAMA.

49. WHO. (2019). Mercury in Skin-Lightening Products: Global Health Alert.

50. SCCS. (2018). Notes of Guidance—Risk Assessment Principles.

51. Felter, S. P., & Nohynek, G. J. (2020). Safety evaluation of cosmetic ingredients. Toxicology Letters, 320.

52. Nohynek, G. J., et al. (2010). Systemic toxicity of cosmetic ingredients. Food and Chemical Toxicology.

53. Api, A. M., et al. (2017). Dermal sensitization quantitative risk assessment (QRA). Regulatory Toxicology and Pharmacology.

54. Rothe, H., et al. (2011). Consumer exposure model for cosmetics. Food and Chemical Toxicology.

55. Patil, V. M., et al. (2010–2017). QSAR modeling applications in toxicity prediction.

56. Sharma, A., et al. (2021). QSAR models for cosmetic ingredient safety. Chemosphere.

57. Maunz, A., et al. (2013). Read-across and QSAR in cosmetics toxicology. Regulatory Toxicology and Pharmacology.

58. Alves, V. M., et al. (2018). Deep learning for toxicity prediction. Frontiers in Environmental Science.

59. Yang, H., et al. (2020). In silico tools for predicting skin sensitization. Journal of Applied Toxicology.

60. OECD. (2019). Good In Vitro Method Practices (GIVIMP).

61. ECHA. (2017). Read-Across Assessment Framework (RAAF).

62. Basketter, D. A., et al. (2014). Skin sensitization risk assessment. Regulatory Toxicology and Pharmacology.

63. Jaworska, J., et al. (2013). QSAR applicability domain in regulatory toxicology. ALTEX.

64. Worth, A. P., et al. (2014). Alternative methods for cosmetics safety assessment. Toxicology.