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APPLICATIONS OF QUANTITATIVE STRUCTURE ACTIVITYRELATIONSHIP(QSAR)IN ASSESSING AQUATIC TOXICITY

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Abstract:
Aquatic toxicity is a crucial endpoint for evaluating chemically adverse effects on ecosystems. Increasing industrialization is the potential cause for aquatic toxicity as it introduces harmful effluent to the river or sea or other fresh water system.
Some chemical substances have the potential to enter the coastal and marine environment andcause adverse effects on ecosystems, bioavailability, and human health.
Therefore, we have developed quantitative structure-activity relationship (QSAR)models forvarious individual and mixture data sets for the prediction of the aquatic toxicity.
QSAR models can be used to aid testing prioritization of the thousands of chemical substancesfor which no ecological toxicity data is available. This QSAR models to predict two types of endpoints: acute LC_{50} and points of departure similar to the NOEC models.

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INTRODUCTION:

In an era of rapid industrialization and chemical advancements, the concern surrounding aquatic toxicity has become a paramount issue in the scientific community. Aquatic toxicity entails the adverse effects of various manufactured chemicals, as well as anthropogenic and natural substances, on aquatic organisms and ecosystems across different trophic levels. This article explores the critical importance of evaluating and managing the impact of chemical substances on aquatic environments, with a particular focus on the role of Quantitative Structure-Activity Relationship (QSAR) modeling[1]. QSAR models are instrumental in predicting the toxicological effects of chemicals, including their potential impact on aquatic ecosystems. This article delves into the multifaceted applications of QSAR in the context of aquatic toxicity:

1. Regulatory Compliance: QSAR models aid regulatory agencies in assessing the potential toxicity of chemicals, ensuring their compliance with environmental safety standards.

2. Chemical Risk Assessment: QSAR enables the prediction of hazards associated with chemicals, facilitating risk assessment and management strategies to safeguard aquatic ecosystems.

3. Chemical Design: QSAR sheds light on the structural aspects of chemicals contributing to aquatic toxicity, guiding the design of less harmful compounds.

4. Prioritizing Testing: QSAR assists in prioritizing chemicals for further laboratory testing, optimizing resource allocation.

5. Environmental Monitoring: By predicting the impact of pollutants on aquatic organisms, QSAR models enhance environmental monitoring efforts.

6. Ecological Risk Assessment: QSAR models contribute to understanding the potential ecological risks of chemical exposure at various trophic levels within aquatic ecosystems.

7. Structure Optimization: QSAR informs the optimization of chemical structures to reduce their environmental impact while retaining their functionality.

8. Mechanistic Insights: QSAR aids in understanding the mechanisms through which chemicals exert their toxicity on aquatic organisms.

9. Bioavailability Predictions: QSAR models estimate the bioavailability of chemicals in aquatic environments, a crucial factor in assessing their impact on aquatic life.

10. Emerging Contaminants: QSAR plays a role in identifying and assessing the toxicity of emerging contaminants, such as pharmaceuticals and personal care products, that may enter aquatic systems.

In summary, QSAR serves as a vital tool in the assessment and management of aquatic toxicity. It provides a cost-effective and efficient means of evaluating the potential impact of chemicals on aquatic ecosystems, ensuring the preservation of water resources and aquatic life.

Several QSAR models have been created specifically for aquatic toxicology. ECOSAR is a multispecies QSAR tool including models of acute and chronic lethal concentrations and points of departure created by the EPA.[2]

One of the biggest challenges in QSAR modeling is correctly estimating model performance on new chemicals. Misleading error estimation can arise from using a favorable choice of validation set or from statistical fluctuations, especially when the test set size is small.

Our goal was to create robust multispecies fish toxicity QSAR models to guide testing prioritization. We incorporated as much experimental data as possible to create models with wide applicability domains that would exhibit high predictivity on new data, be less prone to overfitting, and yield a more precise estimate of their uncertainty.

To deal with experimental and interspecies variability, these models include study covariates and a taxonomy-based accounting of species as parts of their feature sets. Two models have been built: one that predicts acute LC_{50} and one that predicts repeat dose NOEC (no observed effect concentration), LOEC (lowest observed effect concentration), MATC (maximum acceptable toxicant concentration), and LC_0 (no observed lethal effect concentration). All reported concentrations and error statistics are given in $\log_{10}$ transformed values (units of mg/L).

quantitative structure-activity relationship (QSAR) models have been developed for ecotoxicity of pharmaceuticals on four different aquatic species namely Pseudokirchneriella subcapitata, Daphnia magna, Oncorhynchus mykiss and Pimephales promelas using genetic algorithm (GA) for feature

selection followed by Partial Least Squares regression technique according to the Organization for Economic Co-operation[3] and Development (OECD) guidelines.

Double cross-validation methodology was employed for selecting suitable models. Only 2D descriptors were used for capturing chemical information [4] and model building, whereas validation of the models was performed by considering various stringent internal and externalvalidation metrics.

Aquatic toxicity

It is the study of the effects of manufactured chemicals and other anthropogenic and natural materials and activities on aquatic organisms at various levels of organization, from subcellular through individual organisms to communities and ecosystems.[5] Aquatic toxicology is a multidisciplinary field which integrates toxicology, aquatic ecology and aquaticchemistry .

This field of study includes fresh water ,marine water and sediment environments. Common tests include standardized acute and chronic toxicity tests lasting 24–96 hours (acute test) to 7 days or more (chronic tests). These tests measure endpoints such as survival, growth, reproduction, that are measured at each concentration in a gradient,[6] along with a control test. Typically using selected organisms with ecologically relevant sensitivity to toxicants and a well-established literature background. These organisms can be easily acquired or cultured in lab and are easy to handle.[7]

History

While basic research in toxicology began in multiple countries in the 1800s, it was not until around the 1930s that the use of acute toxicity testing, especially on fish, was established. Due to the popularity of organochlorine pesticide DDT [l,l,l-trichloro-2,2-bis(p- chlorophenyl)ethane] and its linkage to causing fish death,[8] the field of aquatic toxicology grew. At first, studies focused mainly on oysters and mussels, as they could not move away from the toxic environment. Over the next two decades, the effects of chemicals and wastes on non-human species became more of a public issue and the era of the *pickle-jar bioassays* began as efforts increased to standardize toxicity testing techniques.

In the United States, the passage of the Federal Water Pollution Control Act of 1947 marked the first comprehensive legislation for the control of water pollution and was followed by the Fedaral water pollution control act in 1956. In 1962, public and governmental interests were renewed, in large part due to the publication of Rachel carson's silent spring, and three years later the water quality act of 1965 was passed, which directed states to develop water quality standards. Public awareness, as well as scientific and governmental concern, continued to grow throughout the 1970s and by the end of the decade research had expanded to include hazard evaluation and risk analysis. In the subsequent decades,[9] aquatic toxicology hascontinued to expand and internationalize so that there is now a strong application of toxicity testing for. Environmental protection.

Aquatic toxicology is continuing to evolve as risk assessment is becoming more practiced in the field. The field is gaining popularity as it has begun to link the effects of pollutants on marine animals to humans who eat fish and other marine life.

Regulatory Compliance

Quantitative Structure-Activity Relationship (QSAR) models play a role in predicting aquatic toxicity for regulatory compliance. They assist in evaluating the potential environmental impact of chemicals. Compliance often involves adherence to specific regulatory frameworks, such as the REACH regulation in the European Union or the Toxic Substances Control Act (TSCA) in the United States. QSAR models must meet validation criteria outlined in these regulations to be accepted as reliable tools for assessing aquatic toxicity.[10] Additionally, transparency and documentation of the model's development and validation processes are crucial for regulatory approval**.**

Chemical Risk Assessment

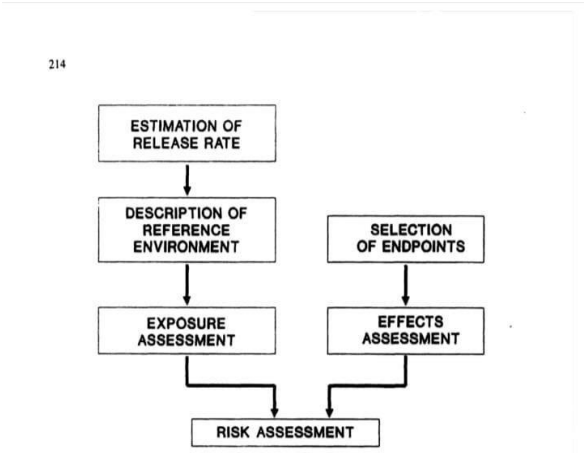
Risk assessment may be defined as the process of assigning magnitudes and probabilities to adverse effects of human activities or natural catastrophes (Barnthouse and Suter 1986). Ecological risk assessment evaluates the probability of the exposure level of potential contaminants to exceed effective, toxic concentrations in the environmental compartment of concern. [11]

Risk assessment deals with the expected environmental concentration-time profile for a chemical at specific locations in various media during manufacture, use, and dissipation of the product that may result In hazard to man and the environment. The necessary Information to judge on environmental hazard and risk, resulting from the use of chemicals, are accessible from field/laboratory studies and various modeling techniques. In ecological risk assessment, uncertainties concerning potential effects must be explicitly recognized and, if possible,

quantified.[12] Quantitative structure activity relationships (QSARs) are a tool to recognize and utilize the systematic relationships between the chemical behaviour and the biological, ecotoxicological, and pharmacological activity of chemicals.

Risk Assessment Procedure

Risk assessment is the attempt to relate exposure and effects processes that in an uncertain orprobaballistic way may result in an undesirable situation, and than of estimating their nature and magnitudethis process is descriptive and analytical,it does not include the peoples and



Flowchart.1. Ecological Risk Assessment

The target of adverse effects is identified and suitable endpoints to quantify these effects are selected, e.g. toxicity to organisms representative for this environment.[13]Based on these information and the respective data the exposure and effect assessment is feasible, serving as input for the risk assessment. QSARs and transport models can be applied .

Chemical design

Industrial ecology has revolutionized our understanding of materials stocks and flows in our economy and society. For this important discipline to have even deeper impact, we must understand the inherent nature of these materials in terms of human health and the environment. [14]This paper focuses on methods to design sympathic chemicals to reduce their intrinsic ability to cause adverse consequence to the biosphere. Advances in the fields of computational chemistry and molecular toxicity in recent decades allow the development of predictive models that inform the design of molecules reduced potential to be toxic to humans or the environment.The approach presented herein builds on the important work qualitative structure – activity relationship by linking toxicological and chemical mechanistic insights to the identification of critical physical - chemical properties needed to be modified.this in silico approach yield guideline Using boundary values for physiochemical properties.acute aquatic toxicity serves as a model endpoint in this study. Defining value ranges for properties related to bioavailability and reactivity eliminates 99% of the chemicals in the highest concern for acute aquatic toxicity category. This approach and its future implementations [15] are expected to yield very powerfultools for life cycle assessment practitioners and molecular designers that allow rapid assessment of multiple environmental and human health end points and inform modifications to minimize hazard.

Qualitatitative structure- activity relationship [QSAR] models play a crucial role in predicting aquatic toxicity of chemicals. They analyze the correlation between the chemical structure and its biological activity. Key molecular descriptors, such as lipophilicity and electronic properties, are considered in QSAR models to understand and predict aquatic toxicity. Experimental data on the toxicity of various chemicals to aquatic organisms are used to train and validate these models,[16] aiding in the design of safer chemicals with reduced environmental impact . Advances in computational chemistry and mechanistic toxicology provide the fundamental knowledge to advance the rational design of chemicals with minimal unintended biological activity. Although risk models are very useful in regulatory decision making, models that can characterize the intrinsic hazard of a chemical can be useful to practitioners of industrial ecology, toxicology, chemistry and engineering.

Development of in silico methods for estimation of toxicity from chemical structures has advanced considerably in recent decades, with significant emphasis on quantitative structure– activity relationships.QSARs have not successfully replaced in vitro and in vivo testing for many endpoints . Further, QSARs are not intended to directly inform chemical design, as they cannot be used to qualitatively assess whether a particular structural modification will result in a different toxicity profile.[17] This information is critical for efficiently and effectively designing alternative chemicals and materials that mitigate toxicity risks across the life. Study study presented here investigates and evaluates a possible approach to the development of a rapid screening tool based on design guidelines for property ranges. The approach differs from QSAR in that rather than predicting a toxicity value or a

threshold, it elucidates the probability that a compound with particular properties will exhibit a certain toxicity profile.

Prioritizing testing

Prioritizing aquatic toxicity testing based on Quantitative Structure-Activity Relationship (QSAR) involves assessing chemical structures to predict their potential impact on aquatic organisms.[18] Consider factors such as structural features, physicochemical properties, and existing data to identify high-risk substances for targeted.

The European regulation on chemicals (REACh) places emphasis on the reduction of systematic toxicity testing, thus fostering the development of alternative methods, such as testing strategies or statistical methods based on existing data. In this context, quantitative structure–activity relationships (QSAR) methods[19] relate the physicochemical properties of chemicals with their toxicity on the basis that similar compounds have similar biological activities or properties (Tropsha, 2010). Many QSAR models predict toxicity with specific descriptors such as the n-octanol/water partition coefficient alone associated with a chemical class as in EcoSAR software, or, depending on the mechanism of toxic action ,associated with other parameters such as the energy of the lowest unoccupied molecular orbital or thedissociation constant, Hammett Co constant, index of valence molecular connectivity, perimeter of the efficient cross-section of molecule, and melting point .[20] other QSAR models rely on generating large sets of descriptors and using statistical methods to reduce dimensionality and identify underlying structural factors influencing toxicity. QSAR models have been made available in various software packages .

Structure–activity relationships (SAR) can take the physicochemical properties into account by considering the functional or chemical class of molecules. [21]Besides considering the overall level of toxicity of a chemical towards each species, studying species' relative sensitivity is particularly relevant in the regulatory context of environmental risk assessment and when considering the avoidance of tests on vertebrate. [22]developed quantitative inter-specific chemical activity relationships (QICAR) for pesticides on algae, daphnids, and fish. The toxicity was related to the functional and chemical class of the compounds and the physicochemical properties also contributed to predicting the toxicity towards one species based on the toxicity towards a different species.[23]

Environmental Monitoring

Quantitative Structure-Activity Relationship (QSAR) models play a crucial role in environmental monitoring of aquatic toxicity by predicting the relationship between chemical structures and their toxic effects. These models aid in assessing potential ecological risks and guiding regulatory decisions based on the molecular characteristics of substance .

Although organic chemicals are often exposed to the environment as a form of chemical mixtures rather than individual compounds,[24] there is insufficient toxicity data available for the chemical mixtures due to the associated complexities. Most importantly, the nature of toxicity of mixtures is completely different from the individual chemicals, which makes the evaluation more difficult and challenging. In this paper, we have developed QSAR models for various individual and mixture data sets for the prediction of the aquatic toxicity.[25] We have used Partial Least Squares (PLS) regression as a statistical tool to build the models.[26] The various structural features of the individual chemicals and the mixture components have been modeled against the toxicity end point pEC50 (negative logarithm of median effective concentration in molar scale) of the aquatic organisms Photobacterium phosphoreum (marine bacterium) and Selenastrum capricornutum (freshwater algae). [27]The mixture descriptors have been calculated by the weighted descriptor generation approach.

Ecological Risk Assessment

In The field of aquatic toxicology, quantitative structure-activity relationships (QSARs) have developed as scientifically credible tools for predicting the toxicity of chemicals when little or no empirical data are available. A fundamental understanding of toxicological principles has been considered an important component to the acceptance and application of QSAR approaches as biologically relevant in ecological risk assessments. As a consequence, there has been an evolution of QSAR development and application from that of a chemical-class perspective to one that is more consistent with assumptions regarding modes of toxic action. In this review, techniques to assess modes of toxic action from chemical structure are discussed, with consideration that toxicodynamic knowledge bases must be clearly defined with regard to exposure regimes, biological models/endpoints and compounds that adequately span the diversity of chemicals anticipated for future applications. With such knowledge bases, classification systems, including rule-based expert systems, have been established for use in predictive aquatic toxicology applications. The establishment of

QSAR techniques that are based on an understanding of toxic mechanisms is needed to provide a link to physiologically based toxicokinetic and toxicodynamic models,[28] which can provide the means to extrapolate adverse effects across species and exposure regimes.

Ecological risk assessments are used by the US Environmental Protection Agency (US EPA) and other governmental agencies to assist in determining the probability and magnitude of deleterious effects of hazardous chemicals on plants and animals. [29]These assessments are important steps in formulating regulatory decisions. The completion of an ecological risk assessment requires the gathering of ecotoxicological hazard and environmental exposure information. This information is evaluated in the risk characterization section to assist in making the final risk assessment.

ASTER (Assessment Tools for the Evaluation of Risk) was designed by the US EPA Environmental Research Laboratory-Duluth (ERL-D) to assist regulators in producing assessments. ASTER is an integration of the AQUIRE (Aquatic toxicity Information Retrieval system) and QSAR (Quantitative Structure Activity Relationships) systems.[30] AQUIRE is a data base of aquatic toxicity tests and QSAR is comprised of a data base of measured physicochemical properties, and various QSAR models that estimate physicochemical and ecotoxicological endpoints. ASTER will be available to international governmental agencies through the US EPA National Computing Center.

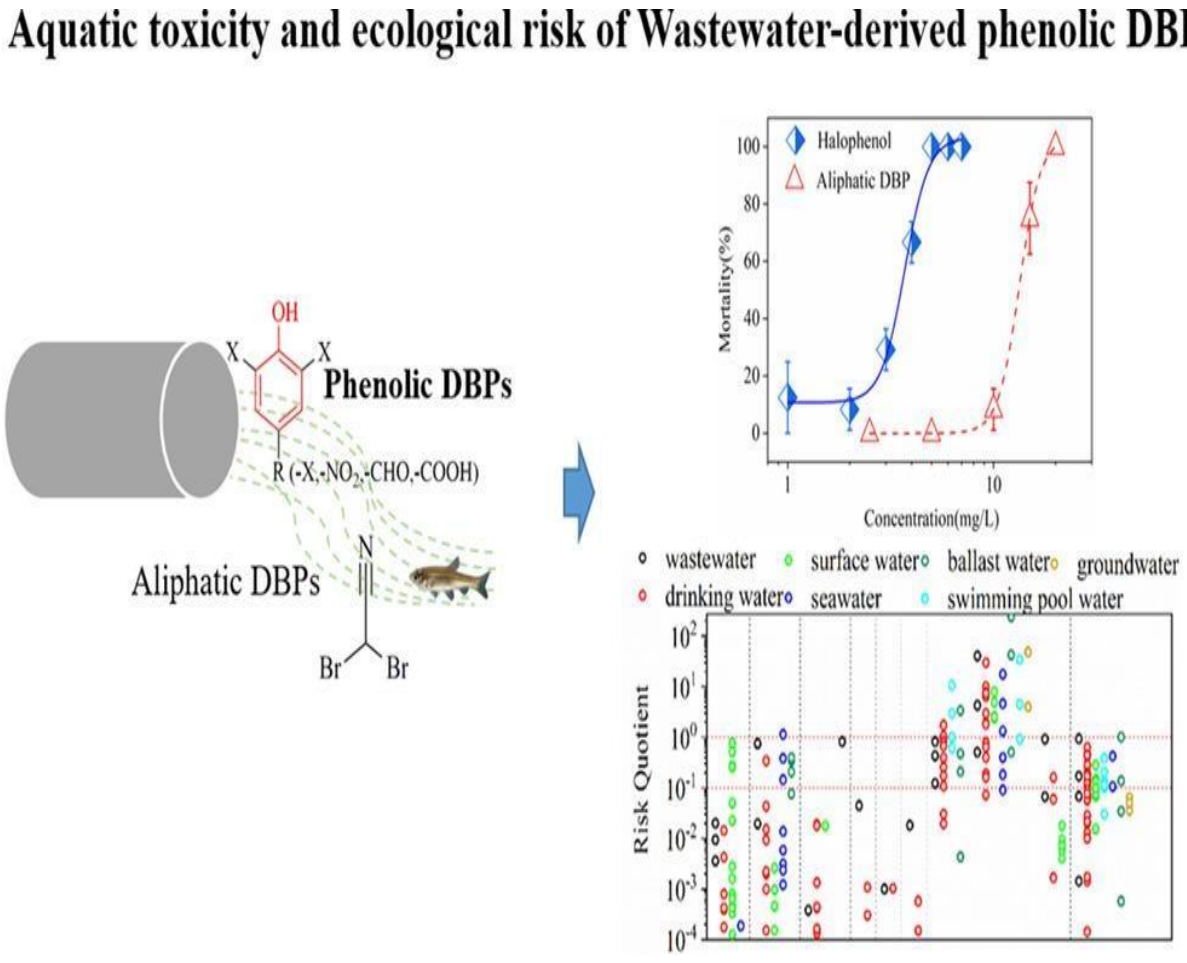


Fig .1. Aquatic toxicity and ecological risk of wastewater- derived phenolic DBPs

Structure optimization

Optimize the structure for aquatic toxicity in QSAR (Quantitative Structure-Activity Relationship), consider refining molecular features, such as substituents, functional groups, or descriptors related to aquatic toxicity. Utilize computational tools to analyze the relationship between chemical structure and toxicity data, adjusting parameters to enhance model accuracy. Iteratively refine the model based on feedback, incorporating diverse datasets for robustness. Experiment with different algorithms and molecular descriptors to uncover the most effective combination for predicting aquatic toxicity.

Investigation of the influence of molecular structure of different organic compounds on acute toxicity towards Fathead minnow, Daphnia magna, and Tetrahymena pyriformis has been carried out using 2D simplex representation of molecular structure and two modelling methods: Random Forest (RF) and Gradient Boosting Machine (GBM). Suitable QSAR (Quantitative Structure – Activity Relationships) models were obtained.[31] The study was focused on QSAR models interpretation. The aim of the study was to develop a set of structural fragments that simultaneously consistently increase toxicity toward Fathead minnow, Daphnia magna, Tetrahymena pyriformis. The interpretation allowed to gain more details about known toxicophores and to propose new fragments. The results obtained made it possible to rank the contributions of molecular fragments to various types of toxicity to aquatic organism.

This information can be used for molecular optimization of chemicals. According to the results of structural interpretation, the most significant common mechanisms of the toxic effect of organic compounds on fathead minnow.

Fig .2.Structural Patterns on Acute Aquatic toxicity of Organic Compounds

Daphnia magna and Tetrahymena pyriformis are reactions of nucleophilic substitution and inhibition of oxidative phosphorylation in mitochondria. In addition acetylcholinesterase and voltage-gated ion channel of Fathead minnow and Daphnia magna are important targets for toxicants. The on-line version of the OCHEM expert system (https://ochem.eu) were used for a comparative QSAR investigation.[32] The proposed QSAR models comply with the OECD principles and can be used to reliably predict acute toxicity of organic compounds towards Fathead minnow, Daphnia magna and Tetrahymena pyriformis with allowance for applicabilitydomain estimation.

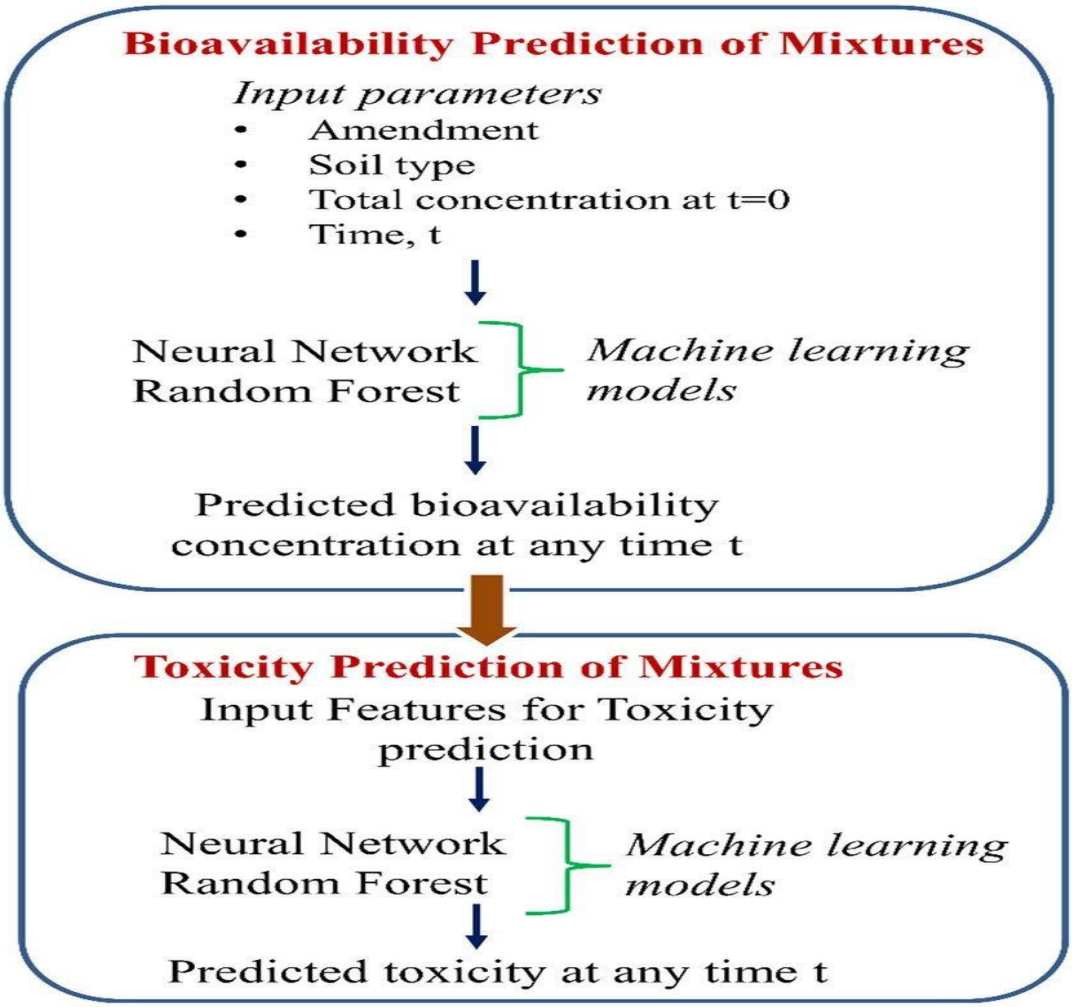
Bioavailability Predictions:

Bioavailability models predicting acute and/or chronic zinc toxicity to a green alga (Pseudokirchneriella subcapitata), a crustacean (Daphnia magna), and a fish (Oncorhynchus mykiss) were evaluated in a series of experiments with spiked natural surface waters. The eight selected freshwater samples had varying levels of bioavailability modifying parameters: pH (5.7-8.4), dissolved organic carbon (DOC, 2.48-22.9 mg/L), Ca (1.5-80 mg/L), Mg (0.79-18 mg/L), and Na (3.8-120 mg/L). In those waters, chronic zinc toxicity (expressed as 10% effective concentrations [EC10]) varied up to 20-fold for the alga (72-h EC10 from 27.3 to 563 microg Zn/L), and approximately sixfold for the crustacean (21-d EC10 from 59.2 to 387 microg Zn/L), and fivefold for the fish (30-d LC10, lethal concentration for 10% of the organisms, from 185 to 902 microg Zn/L). For P. subcapitata a refined bioavailability model was developed by linking an empirical equation, which predicts toxicity expressed as free Zn^{2+} activity as a function of pH, to the geochemical speciation model WHAM/Model V. This model and previously developed acute and/or chronic biotic ligand models for D. magna and 0. mykiss generally predicted most effect concentrations by an error of less than a factor of two.[33] In waters with pH > 8, however, chronic toxicity to D. magna was underestimated by a factor 3 sto 4. Based on the results of this validation exercise and earlier research, we determined applicability ranges for pH (6-8) and Ca (5-160 mg/L) in which all three developed models are valid. Within these ranges, all three models may be considered useful tools for taking into account bioavailability in regulatory assessments of zinc.

Quantitative structure-toxicity relationship (QSTR) models can also be generated using the whole mixture toxicity data. In vivo or in vitro experimentation is an integrated part of whole mixture toxicity assessment . These systems are

based on some statistical techniques, expert systems, and neural networks to relate various biological, physicochemical end points (LC 50
, EC 50 , and so on) with molecular structures in the form of descriptors. The major importanceof in silico methods in mixture toxicity predictions are as follows . (f) It is a reliable method to generate more toxicity data of multicomponent chemical mixtures, and hence it leads to easierrisk assessment of mixtures.

Interactions in mixtures occur in specific combinations of components and doses and are particular to different organisms, causing higher (synergism) or lower (antagonism) toxicity than that predicted by Detecting the possible interactions in chemical mixtures, especially synergisms, is an important and challenging task to enable proper environmental regulation, with theoretical models being a powerful tool to predict and guide experiments in that direction
. However, there is currently no model suitable for use as a standard protocol to predict mixture interactions, mainly due to the variety of detailed information regarding mode of action, metabolism (toxicokinetic and toxicodynamic data) and toxicity of chemicals and the complexity of approaches needed to obtain this data in order to parameterize such predictive data-driven models was underestimated by a factor 3 to 4. Based on the results of this validation exercise and earlier research, we determined applicability ranges for pH (6-8) and Ca (5-160 mg/L) in which all three developed models are valid. Within these ranges, all three models may be considered useful tools for taking into account bioavailability in regulatory assessments of zinc.



Flow chart .2. bioavailability prediction of mixtures

However, the assessment of a mixture's toxicity is much more complex than toxicity evaluation of a single component material or chemical, as the interactions among the individual components of a mixture can significantly change the apparent properties of its components. For instance, the components in a mixture can present additive behaviour of response/effects or may induce either increased (synergistic) or decreased (antagonistic) effects. A recent review by Kar & Leszczynski summarized the advantages of chemo-/nano-informatics methodologies for the prediction of the toxicity of mixtures[34] and multicomponent materials, including thefact that: (i) the in silico methods can be applied for the replacement of animal testing for toxicity purposes; (ii) the developed chemo-/nano-informatics approaches can be applied for the prediction of unknown mixture.

Emerging contaminants

Quantitative Structure-Activity Relationship (QSAR) studies play a crucial role in understanding the potential aquatic toxicity of emerging contaminants. By analyzing the molecular structure of these contaminants, QSAR models can predict their effects on aquatic organisms, aiding in risk assessment and regulatory decision. Some chemical substances have the potential to enter the coastal and marine environment and cause adverse effects on ecosystems, biodiversity and human health. For a large majority of them, their fate and effects are poorly understood as well as their use still unregulated. the United Nations stated in the Ocean Conference of 2017, 40% of the world's population live within 100 km of the coast and 25% of them in coastal areas that are less than 10 m above sea . Coastal areas have an important impact over global economy being the recipient places of approximately 50% of international tourists. The biodiversity of marine ecosystems is also crucial, as they are home to approximately 2 million known species, which may be 9% of all marine species . Nevertheless, the combined effect of growing populations[35] and economic development constitutes threatening the same coastal and marine ecosystems .

Numerous pollutants can reach coastal areas due to human activity in these places. However, these areas are not only affected by the activities that take place there. Some studies establish that up to 80% of the pollution of seas and oceans comes from land-based activities. For decades there has been much research studying the contamination of coastal ecosystems by chemical pollutants of various characteristics.

Emerging Contaminants in Marine Coastal Zones

Aquatic ecosystems are the source and support of most of life on Earth. They also encompass a diverse range of direct or indirect services and goods deemed as essential for human activities. They include food provision, energy, mineral resources, transportation routes, recreational activities and ecological functions (e.g., climate systems). Therefore, all aquatic ecosystems are subject to multiple pressures, competing for usage and impacts derived from human activities, being necessary to develop strategies to protect and maintain, its capacity to continuing the delivery of such services.

The European Union (EU), under the strategy of the European Green Deal, devised a set of policies to achieve its ambition of protection and restoration of biodiversity as well, climate neutrality. The main policies related to aquatic ecosystems are the Marine Strategy Framework Directive3 (MSFD) and the Water Framework Directive (WFD) . Both give high relevance to the monitoring and control of pollutants and substances with the potential to pollute. The MSFD and the WFD were designed as a holistic policy to protect marine and freshwater environments around Europe and enable their sustainable case of marine coastal zones, there is an overlap between both directives, since the main source of contaminants in marine environments are originated in land-based facilities and from freshwater systems. The main pollutants can be divided into two groups, legacy contaminants and contaminants of emerging concern (CEC)[36] . The first encompasses the traditional monitored hazardous substances such as inorganic pollutants as heavy metals (e.g., mercury, lead), radionuclides and organic pollutants (e.g., polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs)). The second is defined as "chemicals that have been detected in the environment, but which are currently not included in regulatory monitoring programs and whose fate and biological impacts are poorly understood".

CECs include substances that are not regulated by EPA or EU Norman network including a diverse range of chemicals and their sub-products that are classified under a variety of group categories. The most common groups are flame retardants, antifoulants, anticorrosion agents, polyfluoroalkyl substances other than PFOS and PFOA, benzotriazoles or siloxanes also, pharmaceuticals, antibiotics, personal care products and illicit drugs, as well as, microplastics,trace metals, nanomaterials and pesticides . While PhaCs have been the most prominent emerging pollutants for decades, PCPs have gained great attention in the last 5-10 years, given the wide and varied use of daily care products by the population. Thus, the focus is nowadays put on

compounds such as parabens or UV filters, which are widely added to PCPs due to theirbenefits, but whose adverse effects are becoming worrying.

Pharmaceuticals:

Since all over the world the number of PhaCs for veterinary and medical health care, as well as growth promotion of livestock, reaches a few thousand, designed for the diagnosis, treatment or prevention of disease and for restoring, correcting or modifying organic functions through the interaction with specific physiological pathways of targeted organisms. Once reaching the marine ecosystems, they may cause a risk to the health of marine organisms acting as stressors on marine ecosystems already impacted by eutrophication, overfishing and climate changes . Different classes and nature of PhaCs, including antibiotics, β-blockers, anti-inflammatories, antiepileptics, lipid lowering agents and antidepressants, lipid lowering agents.

PhaCs have been detected in water resources and aquatic organisms. Various routes, such as excretion and discharge into sewage system on a Continual basis, discharge of effluent directly into river bodies by the manufacturing plant facilities, landfill leachate, industrial effluent, combined sewer overflows, aquaculture facilities- up to 75% of the administered dietary dose of a veterinary medicine, including antibiotics, can be lost to the surrounding environment , animal feedlots and veterinary practices , constitute important vectors for entry of PhaCs in environment and aquatic system.

Being poorly removed by treatment plants and slowly degraded, increased threats derived from increasing trends in urbanization and commercial activity. Reported that over 2.3 billion people live within coastal limits and more than 50% of coastal countries have 80-100% of their total population within 100 km of the coastline. These trends attend suggest the potential for increasing input of human pharmaceuticals into coastal environment and threfore the need to address potential exposure scenario and implications for marine risk assessment of drug residueand their transformation product.

Globally the volume of used medicines reached 4.5 trillion of doses by 2020 with about about50% of the world population consuming more than one dose per person per day in portugal the consumption of antidepressants and anxiolytical is increasing. Two different studies revealed that in 2018 about 25,000 packs of antidressants were sold pre day. [37]On the other hand, medication for anxiety and for the regulazition of sleep are part of the life of one quarter of the portuguese population.

Regarding the ingredients of PCPs, the most urgent issue is identifying the more dangerous substance and find more biodegradable replacement for them. In these, sense it is expected thatcountries will follow the trend driven by several normatives implemented to protect the environment, for example ,the ban o some

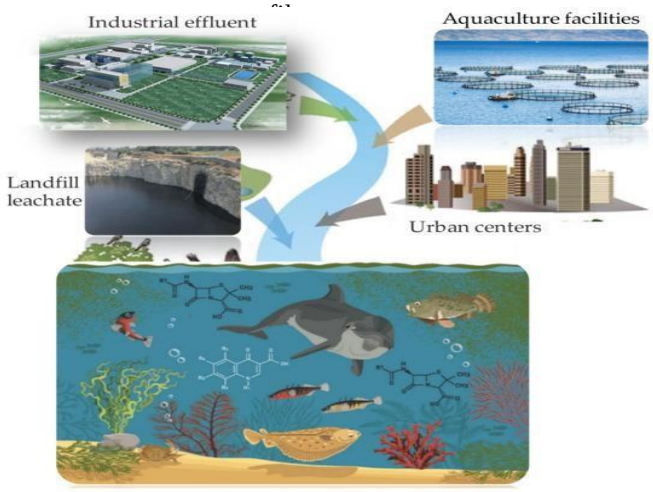


Fig 3 .Typical sources PhaCs and PCPs aquatic system

Being into account site-specific conditions that may influence contaminant bioavailability. An excellent resource for understanding the mechanisms of bioavailability and toxicology of fish is The Toxicology of fishes.

Quantitative Structure-Activity Relationship (QSAR) models can be employed to predict the bioavailability and aquatic toxicity of substances. These models analyze the chemical structureof compounds to make predictions about their biological activity. Consider factors like molecular descriptors, physicochemical properties, and environmental conditions to enhance the accuracy of bioavailability and toxicity predictions in aquatic environmentsthe current study.

various QSAR models were developed for the future prediction of aquatic toxicity and risk assessment of various pharmaceuticals, organic chemicals and their corresponding binary mixtures. Two aquatic organisms, Photobacterium phosphoreum and Selenastrum capricornutum were chosen against which the toxicity data are collected. P. phosphoreum is a gram negative and bioluminescent bacterium living in symbiosis with various marine organisms and a classic marker of the presence of marine toxicants , whereas capricornutum is a type of microalgae of freshwater environment and is

commonly used as a sensitive biomarker of the presence of freshwater toxicants . Negative logarithms of median effective concentration (pEC50) of the chemical species and mixtures were used as the response variable (Y-variable in the data matrix) of the data sets. The weighted descriptor generation approach of binary mixtures has been used to calculate the mixture descriptors in this work. Here, the objectives of the current work are (to identify the maximum possible structural features of the collected data sets of individual chemicals and mixtures responsible for the toxicity; to propose general QSAR models based on the structural features of the individual compounds and the corresponding mixtures; to show the significant structural features in the individual compoundsas well as in the mixture component.

CONCLUSION:

Quantitative Structure-Activity Relationship (QSAR) studies on aquatic toxicity provide valuable insights into the potential impact of chemical substances on aquatic ecosystems. In conclusion, these analyses contribute to our understanding of the structure-activity correlation, helping to predict and assess the toxicity of compounds to aquatic organisms. As we continue to refine QSAR models, they become powerful tools for risk assessment and regulatory decision-making, ultimately supporting efforts to safeguard aquatic environments from harmful chemical exposures.

It explores the importance of the consensus modeling approach when compared with individual QSAR models for prediction of the acute toxicity of pharmaceuticals. The data for model development were collected from widely used ECOTOX (US EPA, 2018) database along withother published literatures.

Prediction of toxicity of various individual chemical data sets and corresponding mixture data sets were accomplished by PLS (partial least squares) regression method. The 2D descriptors were successfully used to measure the contribution of structural features of individual chemicals as well as the components of mixtures to overall toxicity. In addition, the weighted descriptor generation strategy was successfully employed to calculate the mixture descriptors in this work

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