The University of Tehran Press

Pollution

Print ISSN: 2383-451X
Online ISSN: 2383-4501

https://jpoll.ut.ac.ir/

Application of Artificial Intelligence and Machine Learning in Computational Toxicology in Aquatic Toxicology

Mahdi Banaee[1]✉ | Amir Zeidi[1] | Caterina Faggio[2]

1. Aquaculture of Department, Faculty of Natural Resources and the Environment, Behbahan Khatam Alanbia University of Technology, Behbahan, Iran
2. Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy

Article Info

Article type:
Review Article

Article history:
Received: 22 July 2023
Revised: 12 October 2023
Accepted: 20 December 2023

Keywords:
Predictive modeling
QSPR modeling
Data integration and analysis
Toxicity prediction and classification
Data mining and knowledge discovery

ABSTRACT

Computational toxicology is a rapidly growing field that utilizes artificial intelligence (AI) and machine learning (ML) to predict the toxicity of chemical compounds. Computational toxicology is an important tool for assessing the risks associated with the exposure of finfish and shellfish to environmental contaminants. By providing insights into the behavior and effects of these compounds, computational models can help to inform management decisions and protect the health of aquatic ecosystems and the humans who depend on them for food and recreation. In aqua-toxicology research, Quantitative Structure-Activity Relationship (QSAR) models are commonly used to establish the relationship between chemical structures and their aquatic toxicity. Various ML algorithms have been developed to construct QSAR models, including Random Forest (RF), Artificial Neural Networks (ANNs), Support Vector Machines (SVMs), Bayesian networks (BNs), k-Nearest Neighbor (kNN), Probabilistic Neural Networks (PNNs), Naïve Bayes, and Decision Trees. Deep learning techniques, such as Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs), have also been applied in computational toxicology to improve the accuracy of QSAR predictions. Moreover, data mining graphs, networks and graph kernels have been utilized to extract relevant features from chemical structures and improve predictive capabilities. In conclusion, the application of artificial intelligence and machine learning in the field of computational toxicology has immense potential to revolutionize aquatic toxicology research. Through the utilization of advanced algorithms and data analysis techniques, scientists can now better understand and predict the effects of various toxicants on aquatic organisms.

Cite this article: Banaee, M., Zeidi, A., & Faggio, C. (2024). Application of Artificial Intelligence and Machine Learning in Computational Toxicology in Aquatic Toxicology. *Pollution*, 10 (1), 210-235.
https://doi.org/10.22059/poll.2023.362695.2003

DOI: https://doi.org/10.22059/poll.2023.362695.2003

INTRODUCTION

There are many sources of pollution, including agriculture runoff, industrial discharge, sewage and wastewater, oil spills, and plastic wastes, that can contaminate aquatic ecosystems (Banaee et al., 2019; Banaee et al., 2022a, b).

Untreated sewage and wastewater discharged into rivers and oceans can introduce harmful pathogens, viruses, and bacteria and result in water pollution (Ji et al., 2021; Sun et al., 2022). Industries that generate toxic chemicals, heavy metals, or other hazardous materials may discharge these substances into neighboring water sources, leading to water pollution (Derikvandy et al., 2020; Mozafari et al., 2023). The application of pesticides and fertilizers in agriculture can contaminate water sources through leaching and runoff, causing water pollution (Banaee et al., 2013; Banaee et al., 2023a, b). Landfills that do not dispose of waste appropriately

*Corresponding Author Email: *mahdibanaee2@gmail.com*

can contaminate groundwater, which could later enter rivers and other water bodies, resulting in water pollution (Farzaneh et al., 2021; Javahershenas et al., 2022). Accidents such as oil spills from ships or offshore drilling platforms can release excessive quantities of oil into the water and cause severe water pollution (Carpenter, 2019).

Nanoparticle pollution can have significant impacts on water environments, particularly on aquatic ecosystems and the organisms (Banaee et al., 2023; Moore, 2006; Samim et al., 2022). Moreover, nanoparticle pollution can also affect water quality by reducing transparency and increasing turbidity, thereby decreasing light penetration and disrupting photosynthesis (Regier et al., 2015). This can have cascading effects on the food chain, potentially leading to reduced productivity and biodiversity loss.

Plastic pollution is an another of major environmental issue that affects aquatic ecosystems worldwide (Walker & Fequet, 2023; Zeidi et al., 2023). Plastic takes hundreds of years to break down and when it ends up in oceans, rivers, and lakes, it can cause significant harm to marine life and the environment (Gholamhosseini et al., 2023). Plastic waste in the ocean poses a significant threat to marine life as it can often be mistaken for food or cause entanglement resulting in harm or even mortality (Zeidi et al., 2022). Moreover, plastics can release chemicals into the water that can be harmful to aquatic organisms, including endocrine-disrupting chemicals that can interfere with reproductive systems and development (Q. Chen et al., 2019). Plastic pollution can also disrupt the food chain by reducing the availability of food sources for animals, which can have ripple effects throughout the ecosystem (Banaee et al., 2021). Furthermore, accumulations of plastic waste can also damage important habitats such as coral reefs or wetlands, leading to degradation of these ecosystems.

Experimental toxicology can be studied in two broad categories, including in vivo and in vitro. In vivo toxicology involves examining the impact of chemicals on living organisms, typically through animal testing. In contrast, in vitro toxicology entails conducting experiments in a controlled laboratory setting outside of a living organism, such as using isolated cells or tissue cultures (Lacroix et al., 2018; Luijten et al., 2021).

In conducting in vivo toxicology experiments, ethical considerations must be taken into account. One of the main concerns is the use of animals for experimentation, which raises issues about animal welfare and potential harm to living beings (Bruner, 1992; McNamee et al., 2009). To address this, researchers should aim to reduce any pain or discomfort caused during experimentation and adhere to strict regulations and guidelines that prioritize the animals' well-being.

Moreover, there is a growing ethical concern about the necessity of animal testing for toxicology studies (Ceyhan, 2022). Some people argue that subjecting animals to possibly harmful substances is unjustifiable when alternative methods may exist (Pereira & Tettamanti, 2011). Therefore, researchers should also consider exploring other approaches, such as in vitro testing, that minimize the use of animals for toxicity studies.

Although traditional ecotoxicology methods are important tools for assessing the potential risks of chemicals on the environment and aquatic animals' health, they also have several limitations that need to be considered. Hence, new approaches like computational toxicology can offer some advantages over traditional ecotoxicology methods (Netzeva et al., 2007; Modabberi et al., 2020; Silva & Kwok, 2020; Souza et al., 2020), but both approaches should be used as complementary tools for assessing chemical risks.

Since computational toxicology (*in silico*) can replace some animal testing methods (Reisfeld & Mayeno, 2012), researchers should ensure that alternative methods are valid and reliable before phasing out existing techniques that may have been used for many years. It is essential to ensure that any new approach protects human health while reducing animal testing as much as possible. However, ethical considerations in computational toxicology primarily center around data privacy and protection. Since computational toxicology often involves the

use of large datasets, there is a risk that the data collected may contain sensitive information about individuals or groups (Souza et al., 2020). Thus, researchers must ensure that the data is anonymized and protected from potential breaches that could compromise the privacy of those involved. Another ethical concern is the accuracy and transparency of the models used in computational toxicology (Steger-Hartmann, 2013). The efficacy of these models relies on the quality and quantity of data used to train them (Steger-Hartmann, 2013). Therefore, researchers must ensure that the data used does not introduce any biases or inaccuracies that could lead to incorrect predictions or decisions.

Computational toxicology is an emerging field that uses computational tools and artificial intelligence (AI) to predict the toxicity of chemicals and other substances (Choudhuri et al., 2023). This approach can help to reduce the need for animal testing and accelerate the development of safer and more sustainable products.

There are several types of computational tools and AI approaches used in computational toxicology, including Quantitative Structure-Activity Relationship (QSAR) models, high-throughput screening assays, machine learning algorithms, deep learning, and toxicogenomics (Kar & Leszczynski, 2019; Raies & Bajic, 2016; Sarker, 2021; Singh et al., 2023; Wang et al., 2021).

Computational toxicology is an important tool in the assessment of the risks associated with exposure of finfish and shellfish to environmental contaminants. These organisms are often used as sentinel species to monitor the health of aquatic ecosystems, and computational models can help to predict the potential effects of contaminants on these species.

One common application of computational toxicology in finfish and shellfish is in predicting the bioaccumulation of contaminants in these organisms. Bioaccumulation occurs when contaminants accumulate in the tissues of fish and shellfish over time, leading to elevated levels of these compounds in their bodies (Li et al., 2023; Noman et al., 2022; Schmidt & Burgess, 2020). Computational models can help to predict how different contaminants behave in the environment, and how likely they are to accumulate in fish and shellfish (Bartell et al., 2020; Netzeva et al., 2007).

Another use of computational toxicology in finfish and shellfish is in predicting the toxic effects of contaminants on these organisms. Researchers can use computational models to simulate the interactions between contaminants and biological systems, and to predict how exposure to these compounds might affect the health and survival of fish and shellfish. In this study, some of computational methods were briefly introduced that used in aqua-toxicology.

Necessity of using computational toxicology

Computational toxicology is becoming increasingly important in the field of toxicology because it allows for more efficient and cost-effective screening of potentially hazardous chemicals. Traditional toxicological methods involve a significant amount of animal testing, which can be both time-consuming and expensive. Computational toxicology, on the other hand, uses computer models to predict the potential toxicity of chemicals based on their chemical properties and known toxicological data (Kusko & Hong, 2019).

This approach allows researchers to prioritize chemicals for further testing based on their predicted toxicity, reducing the number of animals needed for testing and saving time and resources (Ekins, 2014). Computational toxicology can also help identify potential risks associated with exposure to complex mixtures of chemicals, such as those found in the environment or in consumer products (Wang & Chen, 2019).

Thus, computational toxicology has the potential to significantly improve our ability to identify and mitigate the potential risks associated with exposure to hazardous chemicals, while also reducing the reliance on animal testing (Kusko & Hong, 2019).

Therefore, computational toxicology is becoming an essential tool for predicting the safety

of chemicals, ensuring human and environmental safety, and complying with regulatory requirements.

However, the use of computational toxicology does require specialized infrastructure and tools including advanced computers, database, efficient software, experience and knowledge of programming and modeling, etc. (Lepailleur et al., 2013).

GitHub is a web-based platform that provides a centralized location for software developers to collaborate on projects using the Git version control system (Wheeler et al., 2023). Git allows multiple developers to work on the same codebase simultaneously without stepping on each other's toes, by keeping track of changes made to the code and allowing developers to merge their changes together (Wheeler et al., 2023). GitHub has many potential applications in the field of computational toxicology, as it can be used to facilitate collaboration and open sharing of data and code among researchers.

Researchers can use GitHub (GitHub: Let's build from here · GitHub; https://github.com) to share toxicological data sets they have collected, annotated, or curated with other researchers across different disciplines. This can help to promote the reuse of existing data sets and avoid duplicating efforts (Silva & Kwok, 2022). Furthermore, GitHub can be used to develop and share computational models for predicting toxicity. This could include models that are developed using machine learning or other statistical approaches, as well as more descriptive models that are based on known toxicological mechanisms (Kusko & Hong, 2019). Researchers can collaborate on developing and refining these models, which may ultimately lead to better predictions of toxicity. GitHub can also be used to ensure that research findings are reproducible by others. By sharing code, data, and analysis workflows in a repository, researchers can enable others to replicate their work and verify their findings. This can help to increase the transparency and credibility of computational toxicology research (Silva & Kwok, 2022). Moreover, researchers can use GitHub to develop and share open-source software tools that support the development and application of computational toxicology models (Silva, 2020). Examples of such tools could include libraries for data processing, visualization, and model building, or software packages for running specific types of models. Thus, GitHub can play an important role in advancing the field of computational toxicology by facilitating collaboration, sharing of data and code, and promoting reproducibility and transparency in research.

METHODOLOGY

Quantitative Structure-Activity Relationship

Quantitative Structure-Activity Relationship (QSAR) is a computational approach that establishes a relationship between the chemical structure of a molecule and its biological activity (De et al., 2022; Gramatica, 2020).

The QSAR approach is based on the idea that the properties and activities of molecules are determined by their molecular structures, such as their electronic properties, steric hindrance, and hydrophobicity (Kwon et al., 2019).

The development of QSAR models involves the use of mathematical algorithms to identify and quantify the relationship between structural features and observed activities. These models can then be used to predict the activity of new compounds with similar structures (Tropsha, 2010).

Typically, QSAR models require large datasets of compounds with known activities in order to establish statistically significant relationships (Tropsha, 2010; Z. Wang et al., 2021). The accuracy of QSAR models depends on the quality and quantity of data used to develop them. QSAR models have been successfully applied in the fields of drug discovery, toxicology, environmental chemistry, ecotoxicology and many other areas of research where predicting the activity of molecules is critical (S. Chen et al., 2023; Rácz et al., 2019; Tang et al., 2022;

Table 1. Molecular descriptors in different machine learning models

Model	Model inputs	Molecular descriptors	Performance accuracy (%)	Reference
SVM	1129 (*Tetrahymena pyriformis* toxicity)	CD,PD,GD,CoD,OH	88.90	(Xue et al., 2006)
SVM	611 (fathead minnow toxicity)	CD, ED, PD, TI, GD	95.10	(In et al., 2012)
kNN	1571 (*T. pyriformis* toxicity)	MDL	91.60	(Cheng et al., 2011)
PNN	573 (fathead minnow toxicity)	PD, CD, TD	94.94	(Singh et al., 2013)
NB	151 (diverse pesticides)	FP, Ext, Est, Maccs, Graph, AP2D, …	74	(Li et al., 2017)
kNN	639 (diverse pesticides)	Es, Ext, FP, Gra, Mac, Pub, Sub, …	68.90	(He et al., 2019)
RF	143 (Biocide)	F05, B01, B09, T, ATSC7m, ATSC6s, …	89	(Marzo et al., 2020)

Toropova et al., 2023).

Several stages are involved in constructing a Quantitative Structure-Activity Relationship (QSAR) model based on computational toxicology. These stages include data collection, data preparation, molecular descriptor calculation, model selection, model development, and model validation (Ballabio et al., 2019; Bohlen et al., 2019).

The first step is to collect data on a large number of chemical compounds, along with information about their structural features and biological activities. This data can be obtained from various sources, such as literature databases, public repositories, or experimental studies (Bohlen et al., 2019). Once the data has been collected, it needs to be cleaned, curated, and standardized to ensure its quality and consistency. This may involve removing duplicates, missing values, outliers, or irrelevant variables. The next step is to calculate molecular descriptors for each compound (Bohlen et al., 2019). Molecular descriptors describe various aspects of a chemical's structure, such as size, shape, polarity, and electronic properties (Todeschini & Consonni, 2010). There are several software tools available for calculating molecular descriptors, such as Dragon, RDKit, and PaDEL. Once the molecular descriptors have been calculated, the next step is to select an appropriate modeling technique. There are many machine learning algorithms available for QSAR modeling, including linear regression, support vector machines (SVM), random forest, and neural networks (Jain & Rawat, 2023; Kovačević et al., 2023; Kovács et al., 2021; Trinh et al., 2022). The selection of the modeling technique is dependent on the nature of the data, the intended application, and the researcher's expertise. The selected modeling technique is then used to build a mathematical model that can predict the biological activity or toxicity of new compounds based on their molecular descriptors (Baumann & Baumann, 2014). The model is trained on the curated data set, and model performance is evaluated using cross-validation techniques to assess the accuracy, reliability, and robustness of the model (Kwon et al., 2019). The final step is to validate the QSAR model by applying it to an independent test set of compounds that were not included in the training set. The predicted values are compared with the actual values to evaluate the predictive power of the model (Gramatica & Sangion, 2016). The performance of the model can be further refined by adjusting the model parameters, feature selection or the inclusion of additional descriptors.

Random Forest

Random Forest (RF) is a powerful machine learning technique that is commonly used in computational toxicology to predict the toxicity of chemical compounds (Mistry et al., 2016; Uesawa, 2016). This algorithm falls under the category of supervised learning, where it is trained on a set of data with known outcomes (labels or classes) and then used to predict the outcomes of new data. RF is an ensemble learning method, which means it combines the results of multiple decision trees to generate more accurate predictions (Uesawa, 2016).

In toxicology, RF models can be trained on large sets of chemical data (e.g., physicochemical properties, structural features, etc.) and their corresponding toxicity outcomes (Koutsoukas et al., 2016). These models can then be used to predict the toxicity of new chemicals based on their features. Moreover, RF can be used to predict various endpoints related to toxicity, such as acute toxicity to fishes, mutagenicity, and carcinogenicity (Ospina et al., 2014; Yu & Zeng, 2022). To build an RF model, sometimes thousands of molecular descriptors are calculated for each compound, and these descriptors are used as input features to the model (Kapsiani & Howlin, 2021).

The RF algorithm works by constructing a large number of decision trees, each of which is trained on a randomly selected subset of the input features and a randomly selected subset of the training data (Mistry et al., 2016). The final prediction from the RF model is then generated by averaging the predictions of all the individual decision trees.

One of the advantages of RF is its ability to handle high-dimensional data with many input features (Oo & Thein, 2022). RF can also provide insight into the importance of each input feature for predicting toxicity, which can help researchers understand the underlying mechanisms of toxicity (Jeong & Choi, 2022).

Overall, RF has proven to be a highly effective tool in computational toxicology for predicting toxicity endpoints and prioritizing compounds for further testing. Furthermore, one advantage of using RF in toxicology is that it is highly interpretable (Jia et al., 2023). The algorithm provides information about which features are most important for predicting toxicity, allowing toxicologists to focus on those features for further investigation (Jia et al., 2023). Additionally, Random Forest is robust to noise and outliers in the data.

However, Random Forest models can also suffer from overfitting, where the model becomes too complex and fits the training data too closely, resulting in poor generalization to new data (Hoarau et al., 2023). To avoid overfitting, it is important to tune the hyperparameters of the model and use appropriate cross-validation techniques.

The first step is to preprocess the data. This involves handling missing values, dealing with categorical variables, and scaling the data if necessary. Next, the data needs to be split into training, validation, and test sets (Mooney & Pejaver, 2018). The training set is used to train the model, the validation set is used to tune hyperparameters and prevent overfitting, and the test set is used to evaluate the model's performance.

Before the RF model is built, performing feature selection may be wanted to identify the most important features for predicting toxicity (Koutsoukas et al., 2016; Polishchuk et al., 2009; Svetnik et al., 2003). This can help to reduce the dimensionality of the data and improve the accuracy of the model. Once the data has been preprocessed and split, the RF model can be built. This involves specifying the number of decision trees to include in the ensemble, as well as the maximum depth of each tree and other hyperparameters (Biau & Scornet, 2016). After the RF model has been trained on the training set, its performance should be evaluated on the validation set. This involves calculating various metrics such as accuracy, precision, recall, and F1 score. If the model's performance on the validation set is not satisfactory, tuning the hyperparameters of the RF algorithm may be needed. This can involve adjusting the number of decision trees, the maximum depth of each tree, or other parameters. Once the hyperparameters

Table 2. Random forest modeling studies on different aquatic species

Model	Validation	Toxicity analysis	Target species	Model Input	References
RF	R^2= 0.930	LC_{50}, LD_{50}	*Pimephales promelas*	849 (Insecticide)	(Fei-xiong et al., 2010)
	A= 0.760	Classification of toxicity	*Lepomis macrochirus*	151 (Pesticides)	(Li et al., 2017)
	A= 0.810	LC_{50}	*Lepomis macrochirus*	1906 (chemical compounds)	(Sun et al., 2015)
	A= 0.779		*Pimephales promelas*		
	A= 0.782		*Oncorhynchus mykiss*		
	A= 0.740	EC_{50}	*Daphnia Magna*	639 (chemical compounds)	(He et al., 2019)
	R^2= 0.890	EC_{50}	*Daphnia Magna*	143 (chemical compounds)	(Marzo et al., 2020)

have been tuned and satisfactory performance has been achieved on the validation set, the final model can be evaluated on the test set. This will provide an accurate estimate of how well the model will perform on new, unseen data.

Artificial neural networks

Artificial neural networks (ANNs) have been increasingly used in toxicology for a variety of applications (Green et al., 2021; Pantic et al., 2023; Tetko et al., 2022). ANNs are computational models that are inspired by the structure and function of the human brain. They consist of interconnected nodes (neurons) that process information and learn from data (Silver et al., 2016).

In toxicology, ANNs have been used for prediction of toxicity, classification of compounds based on their toxicity, and analysis of toxicity mechanisms (Noori et al., 2013; Pantic et al., 2023). ANNs have also been employed in the development of quantitative structure-activity relationship (QSAR) models, which are used to predict the toxicity of chemicals based on their molecular structure (Baskin et al., 2009, 2018; Dobchev & Karelson, 2016; Niculescu, 2003; Pantic et al., 2023).

One of the advantages of using ANNs in toxicology is their ability to handle complex, non-linear relationships between chemical structures and toxicity (Vracko, 2006). ANNs can also handle missing or incomplete data and can be trained on large datasets (Krogh, 2008).

However, like all modeling techniques, ANNs have their limitations and require careful validation and interpretation of results. Additionally, the quality of the input data is critical for the accuracy of the ANN model.

Thus, ANNs have proven to be a valuable tool in toxicology research and have the potential to improve our ability to predict and understand chemical toxicity (Asha et al., 2022; Guo & Wang, 2021).

Deep learning is a subset of machine learning that uses neural networks with multiple layers to process and analyze complex data (Dong et al., 2021). Deep learning has become increasingly popular in toxicology research due to its ability to handle large and complex datasets, as well as its capacity to capture non-linear relationships between variables (Heo et al., 2019; Lee & Sung, 2021; Tan et al., 2023; Xu et al., 2022).

In toxicology, deep learning models have been used for drug discovery, toxicity prediction, and chemical structure-activity relationship (SAR) modeling (Matsuzaka & Uesawa, 2023; Meenakshi et al., 2022). For example, deep learning models have been used to predict the

Table 3. Artificial neural networks modeling studies on different aquatic species

Model	Validation	Toxicity analysis	Target species	Model Input	References
ANN	A= 0.790	Classification of toxicity	multispecies	278 (pesticide)	(Li et al., 2017)
	A= 0.810		*Oncorhynchus mykiss*	829 (pesticide)	
PNN	A= 0.940	LC_{50}	*Pimephales promelas*	617 (chemical compounds)	(Singh et al., 2013)
ANN	R^2= 0.880	LC_{50}	*Pimephales promelas*	140 (chemical compounds)	(Huuskonen, 2003)

potential toxicity of new drugs during early-stage development, which can help identify potential safety concerns before expensive and time-consuming clinical trials begin.

Support Vector Machines

Support Vector Machines (SVMs) are a type of machine learning algorithm that have been used in computational toxicology to predict the toxicity of chemical compounds (Wang et al., 2021; Yu, 2021). SVM models work by finding a hyperplane that maximally separates two classes of data, in this case, toxic and non-toxic compounds (Ambure et al., 2021).

In order to develop an SVM model for toxicity prediction, a large dataset of chemical compounds with known toxicities is required. The dataset is split into training and testing sets, and the SVM model is trained on the training set to identify features that differentiate toxic from non-toxic compounds (Jeong & Choi, 2022).

Once the SVM model is trained, it can be used to predict the toxicity of new compounds based on their structural features. SVM models have been successfully applied in various areas of toxicology, including drug discovery, environmental toxicology, and chemical safety assessment (Lin & Chou, 2022; Rodríguez-Pérez & Bajorath, 2022).

However, it is important to note that SVM models are not without limitations. They require a large amount of high-quality data to achieve accurate predictions, and the interpretation of SVM model outputs can be challenging due to their mathematical complexity (Kumar et al., 2019; Waske et al., 2010). Overall, SVMs are a powerful tool in computational toxicology, but their use should be carefully considered and validated.

The first step in using SVMs is to prepare the data. This involves selecting the appropriate training and test datasets, as well as any features or descriptors that will be used to represent the chemicals in the dataset. A critical aspect of using SVMs in computational toxicology is feature generation (Liu et al., 2020). This involves converting the chemical structures into numerical features or descriptors that can be used by the SVM algorithm (Kumar et al., 2019). Some common types of descriptors used in toxicology include molecular weight, logP, and various types of fingerprints (Liu et al., 2020). Once the data has been prepared and the features generated, the next step is to select an appropriate SVM model. There are several different types of SVM models to choose from, including linear, polynomial, radial basis function (RBF), and sigmoid (Armaghani et al., 2020; Saha et al., 2021; Sattlecker et al., 2010; Tanveer et al., 2022). Once a model has been selected, it needs to be trained on the prepared data. During training, the algorithm tries to find the optimal decision boundary that separates the toxic and non-toxic chemicals in the dataset. After training, the model needs to be evaluated on a test dataset to determine its performance (Mammone et al., 2009). Common metrics used to evaluate SVM models in toxicology include accuracy, precision, recall, and F1-score (Kang et al., 2022). If the model's performance is not satisfactory, it may be necessary to optimize the model. This can involve adjusting hyper-parameters or changing the feature set used in modeling. Once the

model has been optimized and tested, it is important to interpret the results. This might involve identifying which features are most important for predicting toxicity or investigating potential mechanisms of toxicity.

Support Vector Machines (SVM) can indeed be used in the field of aquatic toxicology (Ai et al., 2019; Ivanciuc, 2002; Kim et al., 2023; Michielan et al., 2010). Aquatic toxicology focuses on assessing the effects of chemical substances on aquatic organisms and ecosystems (Noori et al., 2012). SVM is a machine learning algorithm that can be employed to develop predictive models for toxicity assessment and classification tasks in aquatic toxicology (Wang et al., 2021; Yu, 2021). SVM can be used to build models that predict the toxicity of chemicals to aquatic organisms (Fan et al., 2021). Researchers typically train SVM models using labeled datasets containing information about chemical properties and corresponding toxicity data. The SVM model can then classify new, unlabeled chemicals based on their features and predict their potential toxicity to aquatic organisms (Xu et al., 2022).

SVM can also be applied to classify exposure levels of aquatic organisms to different chemical pollutants. By training an SVM classifier with input variables such as chemical concentration, exposure duration, and biological responses, it becomes possible to determine the level of toxicity associated with specific exposure scenarios (Ai et al., 2019; Luan et al., 2005; Yu, 2021). Furthermore, SVM models can identify the most important features or descriptors contributing to aquatic toxicity prediction. By examining the SVM's support vectors and associated feature weights, researchers can gain insights into the key chemical properties or characteristics that influence toxicity outcomes. SVM can aid in ecotoxicological risk assessment by integrating diverse datasets (Lee & Sung, 2021). This includes combining chemical properties, environmental factors, and biological response data to evaluate the potential risks posed by different chemicals to aquatic ecosystems. SVM models can help prioritize chemicals for further testing or regulatory actions based on their predicted risk levels.

SVM algorithms can effectively handle high-dimensional data and non-linear relationships, making them suitable for developing QSAR models (Ai et al., 2019; Hakim et al., 2022).

Bayesian networks

Bayesian networks (BNs) are probabilistic graphical models that can be used to represent and analyze complex systems with uncertain relationships between variables. In toxicology, BNs have been used for quantitative risk assessment, predictive toxicity modeling, and prioritization

Table 4. Support vector machine modeling studies on different aquatic species

Model	Validation	Toxicity analysis	Target species	Model Input	References
SVM-GA	R^2= 0.70	pLC_{50}	multispecies	1121 (chemical compounds)	(Yu, 2021)
	R^2= 0.95	$LC_{50,}$ LD_{50}	*Pimephales promelas*	849 (insecticide)	(Fei-xiong et al., 2010)
	A= 0.810	Classification of toxicity	multispecies	278 (pesticide)	(Li et al., 2017)
	A= 0.810		*Oncorhynchus mykiss*	829 (pesticide)	
	A= 0.826		*Lepomis macrochirus*		
SVM	A= 0.733	LC_{50}	*Pimephales promelas*	1906 (chemical compounds)	(Sun et al., 2015)
	A= 0.798		*Oncorhynchus mykiss*		
	A= 0.749	EC_{50}	*Daphnia Magna*	639 (chemical compounds)	(He et al., 2019)
	A= 0.877	LC_{50}	*Pimephales promelas*	617 (chemical compounds)	(Singh et al., 2013)

of chemicals for testing (Langford et al., 2015; Moe et al., 2021).

One advantage of BNs is their ability to handle incomplete and uncertain data, as well as the incorporation of expert knowledge into the model. For example, BNs can be used to integrate information from various sources, such as in vitro and in vivo toxicity data, chemical structure, and physicochemical properties, to predict the potential toxicity of a chemical (Corani et al., 2013).

BNs can also be used for decision-making under uncertainty, for example, by calculating the probability of adverse outcomes based on different exposure scenarios or mitigation strategies. This information can be used to inform regulatory decision-making and risk management (Kovalenko et al., 2019; Sperotto et al., 2019).

However, BNs require careful parameterization and validation, and the quality of the input data is crucial for the accuracy of the model. Additionally, the complexity of the model can make it difficult to interpret the results and identify important causal relationships between variables.

Therefore, BNs are a promising tool for toxicological risk assessment and decision-making, particularly when dealing with complex and uncertain systems (Kovalenko et al., 2019; Moe et al., 2021). However, their use requires an understanding of Bayesian principles and careful consideration of the quality and relevance of the input data.

k-Nearest Neighbor

k-Nearest Neighbor (kNN) is a machine learning algorithm that has been used in computational toxicology to predict the toxicity of chemical compounds (Boone & Di Toro, 2019; Chen et al., 2023; Gajewicz-Skretna et al., 2021). The kNN algorithm works by identifying the k-nearest neighbors of a new compound based on its structural features, and then predicting its toxicity based on the toxicity values of its nearest neighbors (Boone & Di Toro, 2019).

To develop a kNN model for toxicity prediction, a large dataset of chemical compounds with known toxicities is required (Lodhi et al., 2010). The dataset is split into training and testing sets, and the kNN model is trained on the training set to identify the k-nearest neighbors of each compound based on their structural features.

Once the kNN model is trained, it can be used to predict the toxicity of new compounds based on their structural features and their similarity to the compounds in the training set. kNN

Table 5. K.Nearest Neighbor modeling studies on different aquatic species

Model	Validation	Toxicity analysis	Target species	Model Input	References
***GA-k*NN**	R^2= 0.780	LC_{50}	*Daphnia Magna*	546 (organic pollutant)	(Cassotti et al., 2014)
***k*NN**	RMSE= 0.793	LC_{50}	79 (Genus)	1480 (chemical compounds)	(Boone & Di Toro, 2019)
	R^2= 0.99	$LC_{50,}$ LD_{50}	*Pimephales promelas*	849 (insecticide)	(Fei-xiong et al., 2010)
	A= 0.800	Classification of toxicity	multispecies	278 (pesticide)	(Li et al., 2017)
	A= 0.790		*Lepomis macrochirus*	151 (pesticide)	
	A= 0.875		*Lepomis macrochirus*		
	A= 0.752	LC_{50}	*Pimephales promelas*	1906 (chemical compounds)	(Sun et al., 2015)
	A= 0.839		*Oncorhynchus mykiss*		
	A= 0.689	EC_{50}	*Daphnia Magna*	639 (chemical compounds)	(He et al., 2019)

models have been successfully applied in various areas of toxicology, including drug discovery, environmental toxicology, and chemical safety assessment (Meenakshi et al., 2022; Mu'azu & Olatunji, 2023; Wang et al., 2021).

However, it is important to note that kNN models are not without limitations. They require a large amount of high-quality data to achieve accurate predictions, and the choice of k value can significantly affect the performance of the model (Bhatti et al., 2020; Kumar et al., 2022). Additionally, kNN models can be computationally intensive, particularly when working with large datasets. Overall, kNN is a useful machine learning algorithm in computational toxicology, but the application of this method should be carefully considered and validated.

Probabilistic Neural Networks

Probabilistic Neural Networks (PNNs) are a form of machine learning algorithm that have been employed in computational toxicology for predicting the toxicity of chemical compounds (Maertens et al., 2022; Spînu et al., 2022). PNN models work by estimating the probability density function of the feature vectors for each class of compounds, toxic and non-toxic, based on the training set (Mohebali et al., 2019).

To develop a PNN model for toxicity prediction, a large dataset of chemical compounds with known toxicities is required (Born et al., 2023). The dataset is split into training and testing sets, and the PNN model is trained on the training set to estimate the probability density functions of both toxic and non-toxic classes.

Once the PNN model is trained, it can be used to predict the toxicity of new compounds based on their structural features and their probability densities (Ahmadlou & Adeli, 2010). PNN models have been successfully applied in various areas of classification, toxicology, including drug discovery, environmental toxicology, and chemical safety assessment (Andayani et al., 2019; Behzadi et al., 2009; Kaiser et al., 2002).

However, it is important to note that PNN models are not without limitations. They require a large amount of high-quality data to achieve accurate predictions, and the computation of probability densities can be time-consuming. Additionally, PNN models can be sensitive to the choice of kernel function (Singh et al., 2013). Overall, PNNs are a useful machine learning algorithm in computational toxicology, but their application should be carefully considered and validated (Singh et al., 2014).

Naïve Bayes

Naïve Bayes is a type of probabilistic classifier that is commonly used in computational toxicology (Baskin, 2018; Tugcu et al., 2023). It is a machine learning technique that is based on Bayes' theorem, which describes the probability of an event occurring based on prior knowledge or evidence.

In computational toxicology, Naïve Bayes classifiers are often used to predict the toxicity of chemical compounds based on their structural features and other properties (Lin & Chou, 2022). These classifiers work by analyzing the frequency of specific chemical substructures or molecular descriptors that are known to be associated with toxic effects (Zhu et al., 2023).

The underlying assumption of Naïve Bayes is that each feature or descriptor is independent of all others, which is why it is called "naïve"(Webb et al., 2010). Despite this simplifying assumption, Naïve Bayes classifiers can still achieve high accuracy in predicting toxicity, especially when trained on large datasets with diverse chemical structures (Zhang et al., 2017).

Overall, Naïve Bayes classifiers have proven to be a valuable tool in computational toxicology for screening chemical libraries, prioritizing compounds for further testing, and identifying potential toxic mechanisms of action.

Table 6. Naïve Bayes modeling studies on different aquatic species

Model	Validation	Toxicity analysis	Target species	Model Input	References
NB	R^2= 0.750	LC_{50}, LD_{50}	*Pimephales promelas*	849 (pesticide)	(Fei-xiong et al., 2010)
	A= 0.740	Classification of toxicity	*Lepomis macrochirus*	151 (pesticide)	(Li et al., 2017)
	A= 0.650	EC_{50}	*Daphnia Magna*	639 (chemical compounds)	(He et al., 2019)

Decision trees

Decision trees are commonly used in toxicology to help evaluate the potential toxicity of a chemical or substance (Jia et al., 2023; Mistry et al., 2016). The decision tree approach involves breaking down the evaluation process into a series of discrete steps, each of which can be evaluated using available data (Breiman et al., 2017).

The first step in constructing a decision tree for toxicology is to define the problem and the relevant endpoints that need to be considered (Mistry et al., 2016). This may include endpoints such as acute toxicity, irritation, sensitization, or carcinogenicity.

Once the endpoints have been defined, the next step is to gather data on the substance being evaluated, including information on its chemical structure, physical properties, and toxicological effects (Kluxen & Hothorn, 2020). This data can then be used to construct a preliminary decision tree, which outlines the various routes by which the substance could cause harm.

The decision tree can then be refined and revised based on additional data as it becomes available (Kingsford & Salzberg, 2008). For example, if new studies show that the substance has lower toxicity than previously thought, this information can be incorporated into the decision tree to refine the risk assessment (Karim et al., 2019).

Ultimately, the goal of the decision tree approach is to provide a systematic and transparent way of evaluating the potential risks associated with a given substance (Kingsford & Salzberg, 2008). By breaking down the evaluation process into discrete steps, decision trees can help ensure that all relevant factors are considered, and that the risk assessment is based on the best available data.

Deep learning

One of the main challenges in toxicology is predicting the potential adverse effects of chemicals on human health, which can be time-consuming and expensive through traditional experimental methods. Deep learning has been increasingly applied in the field of toxicology to predict toxicity of various chemicals and drugs (Heo et al., 2019; Tandon et al., 2022; Wen et al., 2017).

Deep learning has been applied to the analysis of high-throughput screening data, where thousands of chemicals are tested for their toxicity or activity against specific targets. By identifying patterns in large datasets, deep learning algorithms can help researchers understand the mechanisms underlying toxicity and develop more effective drugs (Heo et al., 2019; Varghese et al., 2020). Furthermore, with deep learning, large amounts of chemical data, including structural information and toxicity profiles, can be processed and analyzed to build predictive models that can forecast potential toxicity (De Vera Mudry et al., 2021). This has the potential to reduce the need for animal testing and accelerate the development of new drugs by quickly identifying compounds with potential toxicities early in the development process. Deep learning models can also be used to identify patterns and relationships between different chemical features and their corresponding toxic effects, leading to insights into the mechanisms

Table 7. Decision tree modeling studies on different aquatic species

Model	Validation	Toxicity analysis	Target species	Model Input	References
DT	R^2= 0.910	LC_{50}, LD_{50}	*Pimephales promelas*	849 (pesticide)	(Fei-xiong et al., 2010)
	A= 0.810	Classification of toxicity	*Lepomis macrochirus*	151 (pesticide)	(Li et al., 2017)
	A= 0.667	EC_{50}	*Daphnia Magna*	639 (chemical compounds)	(He et al., 2019)
	A= 0.916	LC_{50}	*Pimephales promelas*	617 (chemical compounds)	(Singh et al., 2013)
DTbost	A= 0.987	LC_{50}	multispecies	244 (medicinal compounds)	(Singh et al., 2015)
DTforest	A= 0.974				

of toxicity (Cova & Pais, 2019; Jeong & Choi, 2022).

However, deep learning models can be difficult to interpret and may require large amounts of training data to achieve accurate predictions. Additionally, the quality of the input data is critical for the accuracy of the model, and errors in the data can impact the performance of the model (Whang & Lee, 2020).

Therefore, deep learning has demonstrated great potential for advancing toxicology research, and ongoing efforts to improve model accuracy and interpretability will likely lead to even greater use of these techniques in the future.

Convolutional Neural Networks

Convolutional Neural Networks (CNNs) are a type of deep learning model that have gained popularity in recent years due to their success in computer vision tasks such as image classification (Gu et al., 2018). However, CNNs can also be applied to other domains such as computational toxicology (Pantic et al., 2023).

In computational toxicology, CNNs can be used for various tasks such as prediction of toxicity of chemicals, drug safety assessment and identification of potential carcinogens (Kayes et al., 2022; Sun et al., 2019; Yuan et al., 2019). CNNs can learn to identify patterns in the molecular structure of a chemical or drug molecule that may be indicative of its toxicity or safety profile (Miccio & Schwartz, 2020).

For example, a CNN could be trained on a dataset of chemical compounds and their corresponding toxicity levels (Harada et al., 2020). The network would then learn features in the molecular structure of the compounds that are associated with toxicity. Once trained, the CNN could be used to predict the toxicity of new compounds based on their molecular structure.

Another application of CNNs in computational toxicology is in the analysis of high-throughput screening (HTS) data (Idakwo et al., 2019). HTS is a widely used approach for identifying potential drug candidates or toxic compounds by testing large numbers of compounds against biological targets. CNNs can be used to analyze HTS data, allowing researchers to quickly identify patterns and trends in large datasets.

Recurrent Neural Networks

Recurrent Neural Networks (RNNs) have been used successfully in computational toxicology to predict the toxicity of chemicals based on their structure and other properties (Alsenan et al., 2020; Guan, 2023). RNNs are a type of neural network that can process sequences of data, making them well-suited for analyzing chemical structures.

One common application of RNNs in computational toxicology is in predicting the toxicity of new drugs or chemicals (Tan et al., 2023). Researchers can input the chemical structure, as well as other relevant features such as molecular weight and solubility, into an RNN model to predict the toxicity of the compound (Varghese et al., 2020). These models can then be used to prioritize compounds for further testing or to design safer alternatives.

Another use of RNNs in computational toxicology is in predicting the potential side effects of drugs (Segler et al., 2018). By training an RNN model on large datasets of drug interactions and adverse effects, researchers can identify patterns and predict which drugs are more likely to cause certain side effects (Zhang et al., 2018). This information can be used to guide the development of new drugs with fewer side effects.

Data mining graphs and networks

Data mining graphs can be used in toxicology to help identify and analyze patterns in large datasets, which can be useful for predicting toxic effects and understanding the underlying mechanisms of toxicity (Babić et al., 2018; Baskin, 2018). Graph-based data mining techniques, such as network analysis and graph clustering, can be particularly helpful for identifying relationships between different toxicological endpoints, such as gene expression changes or biochemical responses (Cook & Holder, 2000).

One application of data mining graphs in toxicology is the identification of potential drug targets based on their interactions within biological networks (Thafar et al., 2022). By constructing networks of genes, proteins, and other molecules involved in toxicity pathways, researchers can use graph algorithms to identify key nodes within the network that are likely to be important targets for drug development (Takigawa & Mamitsuka, 2013).

Another application of data mining graphs in toxicology is the analysis of chemical structures and their potential toxicological effects (Saigo et al., 2008). By building graphical models of chemical structures and analyzing the relationships between different structural features, researchers can predict how different compounds may interact with biological systems and potentially cause toxicity (Takigawa & Mamitsuka, 2013).

Furthermore, data mining graphs have the potential to be a powerful tool for toxicology research, allowing researchers to discover new insights into the complex relationships between chemicals, biological systems, and toxicity.

Graph kernels

Graph kernels are increasingly being used in the field of molecular toxicology to predict the toxicity of chemical compounds based on their structural similarity to known toxic compounds (Baskin, 2018; Xu et al., 2023). In this context, a graph kernel is a function that takes two graphs as input and computes a similarity score based on their structural properties.

Toxicologists often use chemical structure information to evaluate the hazard potential of chemicals (Nikinmaa, 2014; Rand et al., 2020). In recent years, the use of computational methods to predict toxicity has gained popularity due to its effectiveness, efficiency, and cost-effectiveness compared to traditional experimental methods (Cronin & Yoon, 2018). One such computational method is graph kernels (Yang et al., 2022).

Graph kernels can be used to compare the structural similarities between two molecules by representing them as graphs (Vishwanathan et al., 2010). The nodes of the graph correspond to atoms in the molecule, and the edges represent chemical bonds (Mahé & Vert, 2009). By comparing the structures of different molecules, graph kernels can help identify patterns that are indicative of toxicity.

One example of using graph kernels in toxicology is the prediction of mutagenicity, which is an important factor in determining the safety of chemicals (Swamidass et al., 2005). Mutagens

can cause DNA damage, leading to mutations that can have adverse health effects (Sollazzo et al., 2018). Graph kernels have been used to develop machine learning models that can predict mutagenicity based on the structural features of molecules (Mahé et al., 2005).

Another application of graph kernels in toxicology is the prediction of drug toxicity. Drug toxicity can result in unwanted side effects and can even be life-threatening. Graph kernels have been used to build predictive models that can identify potentially toxic drug candidates based on their chemical structure (Swamidass et al., 2005).

Therefore, graph kernels have shown promise as a tool for predicting toxicity and identifying potential hazards associated with chemical compounds. Their ability to compare structural similarity between molecules can help facilitate the development of safer and more effective drugs and chemicals.

CONCLUSION

The application of artificial intelligence (AI) and machine learning (ML) in computational toxicology has shown great promise in improving our understanding of the effects of chemicals on aquatic organisms. With the increasing concern about the impact of various pollutants on the environment, it is essential to develop accurate and efficient methods to assess the hazards of these chemicals. One of the major advantages of using AI and ML in computational toxicology is their ability to process large amounts of data from various sources quickly and accurately. This enables researchers to identify patterns and relationships between different variables that may not be apparent through traditional methods. In aquatic toxicology, AI and ML can be used to model the effects of a chemical on different species of aquatic organisms, as well as to predict the toxicity of new chemicals based on their chemical structure and properties. These models can help to reduce the need for expensive and time-consuming laboratory experiments, while also providing valuable insights into the mechanisms underlying toxicity. Furthermore, AI and ML can be used to develop more accurate risk assessments for chemicals, taking into account factors such as exposure pathways, bioaccumulation, and ecological interactions. This information can then be used to inform regulatory decisions and improve environmental management practices. Thus, computational toxicology is a powerful tool for assessing the impact of chemicals on fish and shellfish, and can help inform risk assessments and management strategies for protecting these important aquatic species.

GRANT SUPPORT DETAILS

This study was supported by a grant from Behbahan Khatam Alanbia University of Technology, Iran (3-2-6950 BKATU)

CONFLICT OF INTEREST

The authors declare that there is not any conflict of interests regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/ or falsification, double publication and/or submission, and redundancy has been completely observed by the authors.

LIFE SCIENCE REPORTING

No life science threat was practiced in this research.

REFERENCES

Ahmadlou, M., & Adeli, H. (2010). Enhanced probabilistic neural network with local decision circles: A robust classifier. *Integrated Computer-Aided Engineering*, 17(3), 197-210. https://doi.org/10.3233/ICA-2010-0345

Ai, H., Wu, X., Zhang, L., Qi, M., Zhao, Y., Zhao, Q., ... & Liu, H. (2019). QSAR modelling study of the bioconcentration factor and toxicity of organic compounds to aquatic organisms using machine learning and ensemble methods. *Ecotoxicology and environmental safety*, 179, 71-78. https://doi.org/10.1016/j.ecoenv.2019.04.035

Alsenan, S., Al-Turaiki, I., & Hafez, A. (2020). A recurrent neural network model to predict blood–brain barrier permeability. *Computational Biology and Chemistry*, 89, 107377. https://doi.org/10.1016/j.compbiolchem.2020.107377

Ambure, P., Barigye, S. J., & Gozalbes, R. (2021). Machine Learning Approaches in Computational Toxicology Studies. *Chemometrics and Cheminformatics in Aquatic Toxicology*, 125–155. https://doi.org/10.1002/9781119681397.ch7

Andayani, U., Wijaya, A., Rahmat, R. F., Siregar, B., & Syahputra, M. F. (2019, June). Fish species classification using probabilistic neural network. In Journal of Physics: *Conference Series* (Vol. 1235, No. 1, p. 012094). IOP Publishing. https://doi.org/10.1088/1742-6596/1235/1/012094

Jahed Armaghani, D., Asteris, P. G., Askarian, B., Hasanipanah, M., Tarinejad, R., & Huynh, V. V. (2020). Examining hybrid and single SVM models with different kernels to predict rock brittleness. *Sustainability*, 12(6), 2229. https://doi.org/10.3390/su12062229

Asha, P., Natrayan, L. B. T. J. R. R. G. S., Geetha, B. T., Beulah, J. R., Sumathy, R., Varalakshmi, G., & Neelakandan, S. (2022). IoT enabled environmental toxicology for air pollution monitoring using AI techniques. *Environmental research*, *205*, 112574. https://doi.org/10.1016/j.envres.2

Babić, S., Barišić, J., Stipaničev, D., Repec, S., Lovrić, M., Malev, O., ... & Klobučar, G. (2018). Assessment of river sediment toxicity: Combining empirical zebrafish embryotoxicity testing with in silico toxicity characterization. *Science of the Total Environment*, *643*, 435-450. https://doi.org/10.1016/j.scitotenv.2018.06.124

Ballabio, D., Grisoni, F., Consonni, V., & Todeschini, R. (2019). Integrated QSAR models to predict acute oral systemic toxicity. *Molecular informatics*, *38*(8-9), 1800124. https://doi.org/10.1002/minf.201800124

Banaee, M., Beitsayah, A., Prokić, M.D., Petrović, T.G., Zeidi, A. & Faggio, C. (2023a). Effects of cadmium chloride and biofertilizer (Bacilar) on biochemical parameters of freshwater fish, Alburnus mossulensis. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, *268*, 109614. https://doi.org/10.1016/j.cbpc.2023.109614

Banaee, M., Faraji, J., Amini, M., Multisanti, C. R., & Faggio, C. (2023b). Rainbow trout (Oncorhynchus mykiss) physiological response to microplastics and enrofloxacin: novel pathways to investigate microplastic synergistic effects on pharmaceuticals. *Aquatic Toxicology*, 106627. https://doi.org/10.1016/j.aquatox.2023.106627

Banaee, M., Gholamhosseini, A., Sureda, A., Soltanian, S., Fereidouni, M. S., & Ibrahim, A. T. A. (2021). Effects of microplastic exposure on the blood biochemical parameters in the pond turtle (Emys orbicularis). *Environmental Science and Pollution Research*, *28*, 9221-9234. https://doi.org/10.1007/s11356-020-11419-2

Banaee, M., Impellitteri, F., Evaz-Zadeh Samani, H., Piccione, G., & Faggio, C. (2022a). Dietary arthrospira platensis in rainbow trout (*Oncorhynchus mykiss*): a means to reduce threats caused by CdCl2 exposure?. *Toxics*, *10*(12), 731.

Banaee, M., Sagvand, S., Sureda, A., Amini, M., Haghi, B. N., Sopjani, M., & Faggio, C. (2023c). Evaluation of single and combined effects of mancozeb and metalaxyl on the transcriptional and biochemical response of zebrafish (*Danio rerio*). *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, *268*, 109597. https://doi.org/10.1016/j.cbpc.2023.109597

Banaee, M., Soltanian, S., Sureda, A., Gholamhosseini, A., Haghi, B. N., Akhlaghi, M., & Derikvandy, A. (2019). Evaluation of single and combined effects of cadmium and micro-plastic particles on biochemical and immunological parameters of common carp (Cyprinus carpio). *Chemosphere*, *236*, 124335. https://doi.org/10.1016/j.chemosphere.2019.07.066

Banaee, M., Sureda, A., & Faggio, C. (2022b). Protective effect of protexin concentrate in reducing the toxicity of chlorpyrifos in common carp (*Cyprinus carpio*). *Environmental Toxicology and*

Pharmacology, *94*, 103918. https://doi.org/10.1016/j.etap.2022.103918
Banaee, M., Sureda, A., Mirvaghefi, A. R., & Ahmadi, K. (2013). Biochemical and histological changes in the liver tissue of rainbow trout (Oncorhynchus mykiss) exposed to sub-lethal concentrations of diazinon. *Fish physiology and biochemistry*, *39*, 489-501. https://doi.org/10.1007/s10695-012-9714-1
Banaee, M., Zeidi, A., Sinha, R., & Faggio, C. (2023). Individual and Combined Toxic Effects of Nano-ZnO and Polyethylene Microplastics on Mosquito Fish (Gambusia holbrooki). *Water*, *15*(9), 1660. https://doi.org/10.3390/w15091660
Bartell, S. M., Nair, S. K., Galic, N., & Brain, R. A. (2020). The comprehensive aquatic systems model (CASM): advancing computational capability for ecosystem simulation. *Environmental Toxicology and Chemistry*, *39*(11), 2298-2303. https://doi.org/10.1002/etc.4843
Baskin, I. I. (2018). Machine learning methods in computational toxicology. In *Methods in Molecular Biology*. 119-139. https://doi.org/10.1007/978-1-4939-7899-1_5
Baskin, I. I., Palyulin, V. A., & Zefirov, N. S. (2009). Neural networks in building QSAR models. *Artificial Neural Networks: Methods and Applications*, 133-154. https://doi.org/10.1007/978-1-60327-101-1_8
Baumann, D., & Baumann, K. (2014). Reliable estimation of prediction errors for QSAR models under model uncertainty using double cross-validation. *Journal of cheminformatics*, *6*(1), 1-19. https://doi.org/10.1186/s13321-014-0047-1
Behzadi, S. S., Prakasvudhisarn, C., Klocker, J., Wolschann, P., & Viernstein, H. (2009). Comparison between two types of artificial neural networks used for validation of pharmaceutical processes. *Powder Technology*, *195*(2), 150-157. https://doi.org/10.1016/j.powtec.2009.05.025
Bhatti, U. A., Yuan, L., Yu, Z., Nawaz, S. A., Mehmood, A., Bhatti, M. A., ... & Xiao, S. (2021). Predictive data modeling using sp-kNN for risk factor evaluation in urban demographical healthcare data. *Journal of Medical Imaging and Health Informatics*, *11*(1), 7-14. https://doi.org/10.1166/jmihi.2021.3313
Biau, G., & Scornet, E. (2016). A random forest guided tour. *Test*, *25*, 197-227. https://doi.org/10.1007/s11749-016-0481-7
Bohlen, M. L., Jeon, H. P., Kim, Y. J., & Sung, B. (2019). In silico modeling method for computational aquatic toxicology of endocrine disruptors: A software-based approach using QSAR toolbox. *JoVE (Journal of Visualized Experiments)*, (150), e60054. https://doi.org/10.3791/60054
Boone, K. S., & Di Toro, D. M. (2019). Target site model: Predicting mode of action and aquatic organism acute toxicity using Abraham parameters and feature-weighted k-nearest neighbors' classification. *Environmental toxicology and chemistry*, *38*(2), 375-386. https://doi.org/10.1002/etc.4324
Born, J., Markert, G., Janakarajan, N., Kimber, T. B., Volkamer, A., Martínez, M. R., & Manica, M. (2023). Chemical representation learning for toxicity prediction. *Digital Discovery*. https://doi.org/10.1039/D2DD00099G
Breiman, L., Friedman, J. H., Olshen, R. A., & Stone, C. J. (2017). Classification and regression trees. In *Classification and Regression Trees*. https://doi.org/10.1201/9781315139470
Bruner, L. H. (1992). Alternatives to the use of animals in household product and cosmetic testing. Journal of the American Veterinary Medical Association, 200(5), 669-673.
Carpenter, A. (2019). Oil pollution in the North Sea: the impact of governance measures on oil pollution over several decades. *Hydrobiologia*, *845*(1), 109-127. https://doi.org/10.1007/s10750-018-3559-2
Cassotti, M., Ballabio, D., Consonni, V., Mauri, A., Tetko, I. V, & Todeschini, R. (2014). Prediction of acute aquatic toxicity toward daphnia magna by using the ga-k nn method. *Alternatives to Laboratory Animals*, *42*(1), 31–41. https://doi.org/10.1177/026119291404200106
Ceyhan, B. (2022). Assessing the ethical concerns of science and biology teachers regarding regarding animal experimentation _ *Contemporary Educational Researches Journal. 12 (3), 167–176*.
Chen, M., Liu, J., Liao, T. J., Ashby, K., Wu, Y., Wu, L., ... & Hong, H. (2023). Computational Modeling for the Prediction of Hepatotoxicity Caused by Drugs and Chemicals. In *Machine Learning and Deep Learning in Computational Toxicology* (pp. 541-561). https://doi.org/10.1007/978-3-031-20730-3_23
Chen, Q., Allgeier, A., Yin, D., & Hollert, H. (2019). Leaching of endocrine disrupting chemicals from marine microplastics and mesoplastics under common life stress conditions. *Environment international*, *130*, 104938. https://doi.org/10.1016/j.envint.2019.104938

Chen, S., Sun, G., Fan, T., Li, F., Xu, Y., Zhang, N., Zhao, L., & Zhong, R. (2023). Ecotoxicological QSAR study of fused/non-fused polycyclic aromatic hydrocarbons (FNFPAHs): Assessment and priority ranking of the acute toxicity to Pimephales promelas by QSAR and consensus modeling methods. *Science of The Total Environment*, *876*, 162736. https://doi.org/10.1016/j.scitotenv.2023.162736

Cheng, F., Shen, J., Yu, Y., Li, W., Liu, G., Lee, P. W., & Tang, Y. (2011). In silico prediction of Tetrahymena pyriformis toxicity for diverse industrial chemicals with substructure pattern recognition and machine learning methods. *Chemosphere*, *82*(11), 1636-1643. https://doi.org/10.1016/j.chemosphere.2010.11.043

Choudhuri, S., Yendluri, M., Poddar, S., Li, A., Mallick, K., Mallik, S., & Ghosh, B. (2023). Recent Advancements in Computational Drug Design Algorithms through Machine Learning and Optimization. *Kinases and Phosphatases*, *1*(2), 117–140. https://doi.org/10.3390/kinasesphosphatases1020008

Cook, D. J., & Holder, L. B. (2000). Graph-based data mining. *IEEE Intelligent Systems and Their Applications*, *15*(2), 32-41. https://doi.org/10.1109/5254.850825

Corani, G., Magli, C., Giusti, A., Gianaroli, L., & Gambardella, L. M. (2013). A Bayesian network model for predicting pregnancy after in vitro fertilization. *Computers in biology and medicine*, *43*(11), 1783-1792. https://doi.org/10.1016/j.compbiomed.2013.07.035

Cova, T. F., & Pais, A. A. (2019). Deep learning for deep chemistry: optimizing the prediction of chemical patterns. *Frontiers in chemistry*, *7*, 809. https://doi.org/10.3389/fchem.2019.00809

Cronin, M. T., & Yoon, M. (2019). Computational methods to predict toxicity. In *The history of alternative test methods in toxicology* (pp. 287-300). Academic Press. https://doi.org/10.1016/B978-0-12-813697-3.00031-7

De, P., Kar, S., Ambure, P., & Roy, K. (2022). Prediction reliability of QSAR models: an overview of various validation tools. *Archives of Toxicology*, *96*(5), 1279-1295. https://doi.org/10.1007/s00204-022-03252-y

De Vera Mudry, M. C., Martin, J., Schumacher, V., & Venugopal, R. (2021). Deep learning in toxicologic pathology: a new approach to evaluate rodent retinal atrophy. *Toxicologic Pathology*, *49*(4), 851-861. https://doi.org/10.1177/0192623320980674

Derikvandy, A., Pourkhabbaz, H. R., Banaee, M., Sureda, A., Haghi, N., & Pourkhabbaz, A. R. (2020). Genotoxicity and oxidative damage in zebrafish (Danio rerio) after exposure to effluent from ethyl alcohol industry. *Chemosphere*, *251*, 126609. https://doi.org/10.1016/j.chemosphere.2020.126609

Dobchev, D., & Karelson, M. (2016). Have artificial neural networks met expectations in drug discovery as implemented in QSAR framework? *Expert opinion on drug discovery*, *11*(7), 627-639. https://doi.org/10.1080/17460441.2016.1186876

Dong, S., Wang, P., & Abbas, K. (2021). A survey on deep learning and its applications. *Computer Science Review*, *40*, 100379. https://doi.org/10.1016/j.cosrev.2021.100379

Ekins, S. (2014). Progress in computational toxicology. *Journal of pharmacological and toxicological methods*, *69*(2), 115-140. https://doi.org/10.1016/j.vascn.2013.12.003

Fan, J., Huang, G., Chi, M., Shi, Y., Jiang, J., Feng, C., ... & Xu, Z. (2021). Prediction of chemical reproductive toxicity to aquatic species using a machine learning model: An application in an ecological risk assessment of the Yangtze River, China. *Science of The Total Environment*, *796*, 148901. https://doi.org/10.1016/j.scitotenv.2021.148901

Farzaneh, G., Khorasani, N., Ghodousi, J., & Panahi, M. (2021). Assessment of surface and groundwater resources quality close to municipal solid waste landfill using multiple indicators and multivariate statistical methods. *International Journal of Environmental Research*, *15*, 383-394. https://doi.org/10.1007/s41742-020-00307-9

Fei-xiong, C., Jie, S., Wei-hua, L. I., & Yun, T. (2010). In silico prediction of terrestrial and aquatic toxicities for organic chemicals. *Journal of Pesticide Science*, *12*(4), 477–488.

Gajewicz-Skretna, A., Furuhama, A., Yamamoto, H., & Suzuki, N. (2021). Generating accurate in silico predictions of acute aquatic toxicity for a range of organic chemicals: Towards similarity-based machine learning methods. *Chemosphere*, *280*, 130681. https://doi.org/10.1016/j.chemosphere.2021.130681

Gholamhosseini, A., Banaee, M., Sureda, A., Timar, N., Zeidi, A., & Faggio, C. (2023). Physiological response of freshwater crayfish, Astacus leptodactylus exposed to polyethylene microplastics at different temperature. *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, *267*, 109581. https://doi.org/10.1016/j.cbpc.2023.109581

Gramatica, P. (2020). Principles of QSAR modeling: comments and suggestions from personal experience. *International Journal of Quantitative Structure-Property Relationships (IJQSPR)*, *5*(3), 61-97. https://doi.org/10.4018/ijqspr.20200701.oa1

Gramatica, P., & Sangion, A. (2016). A historical excursus on the statistical validation parameters for QSAR models: a clarification concerning metrics and terminology. *Journal of chemical information and modeling*, *56*(6), 1127-1131. https://doi.org/10.1021/acs.jcim.6b00088

Green, A. J., Mohlenkamp, M. J., Das, J., Chaudhari, M., Truong, L., Tanguay, R. L., & Reif, D. M. (2021). Leveraging high-throughput screening data, deep neural networks, and conditional generative adversarial networks to advance predictive toxicology. *PLOS Computational Biology*, *17*(7), e1009135. https://doi.org/10.1371/journal.pcbi.1009135

Gu, J., Wang, Z., Kuen, J., Ma, L., Shahroudy, A., Shuai, B., ... & Chen, T. (2018). Recent advances in convolutional neural networks. *Pattern recognition*, *77*, 354-377. https://doi.org/10.1016/j.patcog.2017.10.013

Guan, M. (2023). Machine Learning for Analyzing Drug Safety in Electronic Health Records. In *Machine Learning and Deep Learning in Computational Toxicology* (pp. 595–610). Springer. https://doi.org/10.1007/978-3-031-20730-3_26

Guo, X., & Wang, J. (2021). Projecting the sorption capacity of heavy metal ions onto microplastics in global aquatic environments using artificial neural networks. *Journal of Hazardous Materials*, *402*, 123709. https://doi.org/10.1016/j.jhazmat.2020.123709

Hakim, R. A., Aditsania, A., & Kurniawan, I. (2022). QSAR Study on Aromatic Disulfide Compounds as SARS-CoV Mpro Inhibitor Using Genetic Algorithm-Support Vector Machine. *Kinetik: Game Technology, Information System, Computer Network, Computing, Electronics, and Control*. https://doi.org/10.22219/kinetik.v7i2.1428

Harada, S., Akita, H., Tsubaki, M., Baba, Y., Takigawa, I., Yamanishi, Y., & Kashima, H. (2020). Dual graph convolutional neural network for predicting chemical networks. *BMC bioinformatics*, *21*, 1-13. https://doi.org/10.1186/s12859-020-3378-0

He, L., Xiao, K., Zhou, C., Li, G., Yang, H., Li, Z., & Cheng, J. (2019). Insights into pesticide toxicity against aquatic organism: QSTR models on Daphnia Magna. *Ecotoxicology and environmental safety*, *173*, 285-292. https://doi.org/10.1016/j.ecoenv.2019.02.014

Heo, S., Safder, U., & Yoo, C. (2019). Deep learning driven QSAR model for environmental toxicology: effects of endocrine disrupting chemicals on human health. *Environmental Pollution*, *253*, 29-38. https://doi.org/10.1016/j.envpol.2019.06.081

Hoarau, A., Martin, A., Dubois, J. C., & Le Gall, Y. (2023). Evidential Random Forests. *Expert Systems with Applications*, *230*, 120652. https://doi.org/10.1016/j.eswa.2023.120652

Huuskonen, J. (2003). QSAR modeling with the electrotopological state indices: predicting the toxicity of organic chemicals. *Chemosphere*, *50*(7), 949-953. https://doi.org/10.1016/S0045-6535(02)00172-8

Idakwo, G., Thangapandian, S., Luttrell IV, J., Zhou, Z., Zhang, C., & Gong, P. (2019). Deep learning-based structure-activity relationship modeling for multi-category toxicity classification: a case study of 10K Tox21 chemicals with high-throughput cell-based androgen receptor bioassay data. *Frontiers in physiology*, *10*, 1044. https://doi.org/10.3389/fphys.2019.01044

In, Y. Y., Lee, S. K., Kim, P. J., & No, K. T. (2012). Prediction of acute toxicity to fathead minnow by local model based QSAR and global QSAR approaches. *Bulletin of the Korean Chemical Society*, *33*(2), 613-619. https://doi.org/10.5012/bkcs.2012.33.2.613

Ivanciuc, O. (2002). Support vector machine identification of the aquatic toxicity mechanism of organic compounds. *Internet Electron. J. Mol. Des*, *1*, 157–172.

Jain, B., & Rawat, R. (2023). QSAR and ANN-based molecular modeling. In *Computational Modelling and Simulations for Designing of Corrosion Inhibitors* (pp. 183–199). Elsevier. https://doi.org/10.1016/B978-0-323-95161-6.00006-0

Javahershenas, M., Nabizadeh, R., Alimohammadi, M., & Mahvi, A. H. (2022). The effects of Lahijan landfill leachate on the quality of surface and groundwater resources. *International Journal of Environmental Analytical Chemistry*, *102*(2), 558-574. https://doi.org/10.1080/03067319.2020.1724984

Jeong, J., & Choi, J. (2022). Artificial intelligence-based toxicity prediction of environmental chemicals: future directions for chemical management applications. *Environmental Science & Technology*, *56*(12), 7532-7543. https://doi.org/10.1021/acs.est.1c07413

Ji, M., Liu, Z., Sun, K., Li, Z., Fan, X., & Li, Q. (2021). Bacteriophages in water pollution control:

Advantages and limitations. *Frontiers of Environmental Science & Engineering*, *15*, 1-15. https://doi.org/10.1007/s11783-020-1378-y

Jia, X., Wang, T., & Zhu, H. (2023). Advancing Computational Toxicology by Interpretable Machine Learning. *Environmental Science & Technology*. https://doi.org/10.1021/acs.est.3c00653

Kaiser, K. L. E., Niculescu, S. P., & Schultz, T. W. (2002). Probabilistic neural network modeling of the toxicity of chemicals to Tetrahymena pyriformis with molecular fragment descriptors. *SAR and QSAR in Environmental Research*, *13*(1), 57-67. https://doi.org/10.1080/10629360290002217

Kang, H. S., Choi, Y. S., Yu, J. S., Jin, S. W., Lee, J. M., & Kim, Y. J. (2022). Hyperparameter Tuning of OC-SVM for Industrial Gas Turbine Anomaly Detection. *Energies*, *15*(22), 8757. https://doi.org/10.3390/en15228757

Kapsiani, S., & Howlin, B. J. (2021). Random forest classification for predicting lifespan-extending chemical compounds. *Scientific reports*, *11*(1), 13812. https://doi.org/10.1038/s41598-021-93070-6

Kar, S., & Leszczynski, J. (2019). Exploration of computational approaches to predict the toxicity of chemical mixtures. *Toxics*, *7*(1), 15. https://doi.org/10.3390/toxics7010015

Karim, A., Mishra, A., Newton, M. A. H., & Sattar, A. (2019). Efficient toxicity prediction via simple features using shallow neural networks and decision trees. *Acs Omega*, *4*(1), 1874–1888. https://doi.org/10.1021/acsomega.8b03173

Kayes, M. I., Prome, R. F., Noor, M., Bhowmik, S., & Ahmed, M. (2022). An Efficient and Lightweight Convolutional Neural Network for Carcinogenic Polyp Identification. *2022 International Conference on Innovations in Science, Engineering and Technology, ICISET 2022*. https://doi.org/10.1109/ICISET54810.2022.9775824

Kim, J., Yuk, H., Choi, B., Yang, M., Choi, S., Lee, K.-J., Lee, S., & Heo, T.-Y. (2023). New machine learning-based automatic high-throughput video tracking system for assessing water toxicity using Daphnia Magna locomotory responses. *Scientific Reports*, *13*(1), 3530. https://doi.org/10.1038/s41598-023-27554-y

Kingsford, C., & Salzberg, S. L. (2008). What are decision trees?. *Nature biotechnology*, *26*(9), 1011-1013. https://doi.org/10.1038/nbt0908-1011

Kluxen, F. M., & Hothorn, L. A. (2020). Alternatives to statistical decision trees in regulatory (eco-) toxicological bioassays. *Archives of toxicology*, *94*(4), 1135-1149.https://doi.org/10.1007/s00204-020-02690-w

Koutsoukas, A., St. Amand, J., Mishra, M., & Huan, J. (2016). Predictive toxicology: modeling chemical induced toxicological response combining circular fingerprints with random forest and support vector machine. *Frontiers in Environmental Science*, *4*, 11. https://doi.org/10.3389/fenvs.2016.00011

Kovačević, S., Banjac, M. K., Podunavac-Kuzmanović, S., Ajduković, J., Salaković, B., Rárová, L., ... & Ivanov, M. (2023). Local QSAR modeling of cytotoxic activity of newly designed androstane 3-oximes towards malignant melanoma cells. *Journal of Molecular Structure*, *1283*, 135272. https://doi.org/10.1016/j.molstruc.2023.135272

Kovács, D., Király, P., & Tóth, G. (2021). Sample-size dependence of validation parameters in linear regression models and in QSAR. *SAR and QSAR in Environmental Research*, *32*(4), 247-268. https://doi.org/10.1080/1062936X.2021.1890208

Kovalenko, I., Davydenko, Y., & Shved, A. (2019). Modeling uncertain situations in decision-making with influence diagrams. In *CEUR Workshop Proceedings* (pp. 106-115).

Krogh, A. (2008). What are artificial neural networks?. *Nature biotechnology*, *26*(2), 195-197. https://doi.org/10.1038/nbt1386

Kumar, B., Vyas, O. P., & Vyas, R. (2019). A comprehensive review on the variants of support vector machines. *Modern Physics Letters B*, *33*(25), 1950303. https://doi.org/10.1142/S0217984919503032

Kumar, K. P., Pravalika, A., Sheela, R. P., & Vishwam, Y. (2022, May). Disease Prediction Using Machine Learning Algorithms KNN and CNN. In *IJRASET* (p. IJRASET42214). https://doi.org/10.22214/ijraset.2022.42214

Kusko, R., & Hong, H. (2019). Computational toxicology promotes regulatory science. In *Advances in Computational Toxicology: Methodologies and Applications in Regulatory Science* (pp. 1-11). Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-16443-0_1

Kwon, S., Bae, H., Jo, J., & Yoon, S. (2019). Comprehensive ensemble in QSAR prediction for drug discovery. *BMC bioinformatics*, *20*(1), 1-12. https://doi.org/10.1186/s12859-019-3135-4

Lacroix, G., Koch, W., Ritter, D., Gutleb, A. C., Larsen, S. T., Loret, T., ... & Kooter, I. (2018). Air–liquid interface in vitro models for respiratory toxicology research: consensus workshop and

recommendations. *Applied in vitro toxicology*, *4*(2), 91-106. https://doi.org/10.1089/aivt.2017.0034
Langford, A. M., Bolton, J. R., Carlin, M. G., & Palmer, R. (2015). Post-mortem toxicology: A pilot study to evaluate the use of a Bayesian network to assess the likelihood of fatality. *Journal of forensic and legal medicine*, *33*, 82-90. https://doi.org/10.1016/j.jflm.2015.04.013
Oh Lee, Y., & Sung, B. (2021). In silico platforms for predictive ecotoxicology: From machine learning to deep learning. *Chemometrics and Cheminformatics in Aquatic Toxicology*, 453-471. https://doi.org/10.1002/9781119681397.ch23
Lepailleur, A., Poezevara, G., & Bureau, R. (2013). Automated detection of structural alerts (chemical fragments) in (eco) toxicology. *Computational and structural biotechnology journal*, *5*(6), e201302013. https://doi.org/10.5936/csbj.201302013
Li, F., Fan, D., Wang, H., Yang, H., Li, W., Tang, Y., & Liu, G. (2017). In silico prediction of pesticide aquatic toxicity with chemical category approaches. *Toxicology research*, *6*(6), 831-842. https://doi.org/10.1039/c7tx00144d
Li, H., Wang, X., Mai, Y., Lai, Z., & Zeng, Y. (2023). Potential of microplastics participate in selective bioaccumulation of low-ring polycyclic aromatic hydrocarbons depending on the biological habits of fishes. *Science of The Total Environment*, *858*, 159939. https://doi.org/10.1016/j.scitotenv.2022.159939
Lin, Z., & Chou, W. C. (2022). Machine learning and artificial intelligence in toxicological sciences. *Toxicological Sciences*, *189*(1), 7-19. https://doi.org/10.1093/toxsci/kfac075
Liu, B., Li, C.-C., & Yan, K. (2020). DeepSVM-fold: protein fold recognition by combining support vector machines and pairwise sequence similarity scores generated by deep learning networks. *Briefings in Bioinformatics*, *21*(5), 1733–1741. https://doi.org/10.1093/bib/bbz098
Lodhi, H., Muggleton, S., & Sternberg, M. J. (2010). Multi-class Mode of Action Classification of Toxic Compounds Using Logic Based Kernel Methods. *Molecular Informatics*, *29*(8-9), 655-664. https://doi.org/10.1002/minf.201000083
Luan, F., Zhang, R., Zhao, C., Yao, X., Liu, M., Hu, Z., & Fan, B. (2005). Classification of the carcinogenicity of N-nitroso compounds based on support vector machines and linear discriminant analysis. *Chemical research in toxicology*, *18*(2), 198-203. https://doi.org/10.1021/tx049782q
Luijten, M., Wackers, P. F., Rorije, E., Pennings, J. L., & Heusinkveld, H. J. (2020). Relevance of in vitro transcriptomics for in vivo mode of action assessment. *Chemical Research in Toxicology*, *34*(2), 452-459. https://doi.org/10.1021/acs.chemrestox.0c00313
Maertens, A., Golden, E., Luechtefeld, T. H., Hoffmann, S., Tsaioun, K., & Hartung, T. (2022). Probabilistic risk assessment–the keystone for the future of toxicology. *Altex*, *39*(1), 3. https://doi.org/10.14573/altex.2201081
Maertens, A., Golden, E., Luechtefeld, T. H., Hoffmann, S., Tsaioun, K., & Hartung, T. (2022). Probabilistic risk assessment–the keystone for the future of toxicology. *Altex*, *39*(1), 3. https://doi.org/10.1016/B978-0-12-816514-0.00014-X
Mahé, P., & Vert, J. P. (2009). Graph kernels based on tree patterns for molecules. *Machine learning*, *75*(1), 3-35. https://doi.org/10.1007/s10994-008-5086-2
Mahé, P., Ueda, N., Akutsu, T., Perret, J. L., & Vert, J. P. (2005). Graph kernels for molecular structure−activity relationship analysis with support vector machines. *Journal of chemical information and modeling*, *45*(4), 939-951. https://doi.org/10.1021/ci050039t
Mammone, A., Turchi, M., & Cristianini, N. (2009). Support vector machines. *Wiley Interdisciplinary Reviews: Computational Statistics*, *1*(3), 283–289. https://doi.org/10.1002/wics.49
Marzo, M., Lavado, G. J., Como, F., Toropova, A. P., Toropov, A. A., Baderna, D., ... & Benfenati, E. (2020). QSAR models for biocides: The example of the prediction of Daphnia magna acute toxicity. *SAR and QSAR in Environmental Research*, *31*(3), 227-243. https://doi.org/10.1080/1062936X.2019.1709221
Matsuzaka, Y., & Uesawa, Y. (2023). Computational Models That Use a Quantitative Structure–Activity Relationship Approach Based on Deep Learning. *Processes*, *11*(4), 1296. https://doi.org/10.3390/pr11041296
McNamee, P., Hibatallah, J., Costabel-Farkas, M., Goebel, C., Araki, D., Dufour, E., ... & Scheel, J. (2009). A tiered approach to the use of alternatives to animal testing for the safety assessment of cosmetics: eye irritation. *Regulatory Toxicology and Pharmacology*, *54*(2), 197-209. https://doi.org/10.1016/j.yrtph.2009.04.004
Meenakshi, D. U., Nandakumar, S., Francis, A. P., Sweety, P., Fuloria, S., Fuloria, N. K., Subramaniyan,

V., & Khan, S. A. (2022). Deep Learning and Site-Specific Drug Delivery: The Future and Intelligent Decision Support for Pharmaceutical Manufacturing Science. *Deep Learning for Targeted Treatments: Transformation in Healthcare*, 1–38. https://doi.org/10.1002/9781119857983.ch1

Miccio, L. A., & Schwartz, G. A. (2020). From chemical structure to quantitative polymer properties prediction through convolutional neural networks. *Polymer*, *193*, 122341. https://doi.org/10.1016/j.polymer.2020.122341

Michielan, L., Pireddu, L., Floris, M., & Moro, S. (2010). Support vector machine (SVM) as alternative tool to assign acute aquatic toxicity warning labels to chemicals. *Molecular informatics*, *29*(1-2), 51-64. https://doi.org/10.1002/minf.200900005

Mistry, P., Neagu, D., Trundle, P. R., & Vessey, J. D. (2016). Using random forest and decision tree models for a new vehicle prediction approach in computational toxicology. *Soft Computing*, *20*, 2967-2979. https://doi.org/10.1007/s00500-015-1925-9

Modabberi, A., Noori, R., Madani, K., Ehsani, A. H., Mehr, A. D., Hooshyaripor, F., & Kløve, B. (2020). Caspian Sea is eutrophying: The alarming message of satellite data. *Environmental Research Letters*, *15*(12), 124047. https://doi.org/10.1088/1748-9326/abc6d3

Moe, S. J., Carriger, J. F., & Glendell, M. (2021). Increased use of Bayesian network models has improved environmental risk assessments. *Integrated Environmental Assessment and Management*, *17*(1), 53-61. https://doi.org/10.1002/ieam.4369

Mooney, S. J., & Pejaver, V. (2018). Big data in public health: terminology, machine learning, and privacy. *Annual review of public health*, *39*, 95-112. https://doi.org/10.1146/annurev-publhealth-040617-014208

Moore, M. N. (2006). Do nanoparticles present ecotoxicological risks for the health of the aquatic environment? *Environment international*, *32*(8), 967-976. https://doi.org/10.1016/j.envint.2006.06.014

Mozafari, Z., Noori, R., Siadatmousavi, S. M., Afzalimehr, H., & Azizpour, J. (2023). Satellite-Based Monitoring of Eutrophication in the Earth's Largest Transboundary Lake. *GeoHealth*, *7*(5), e2022GH000770. https://doi.org/10.1029/2022GH000770

Mu'azu, N. D., & Olatunji, S. O. (2023). K-nearest neighbor based computational intelligence and RSM predictive models for extraction of Cadmium from contaminated soil. *Ain Shams Engineering Journal*, *14*(4), 101944. https://doi.org/10.1016/j.asej.2022.101944

Netzeva, T., Pavan, M., & Worth, A. (2007). Review of data sources, QSARs and integrated testing strategies for aquatic toxicity. In *JRC Scientific and Technical Reports, EUR*. https://publications.jrc.ec.europa.eu/repository/handle/JRC43068

Niculescu, S. P. (2003). Artificial neural networks and genetic algorithms in QSAR. *Journal of molecular structure: THEOCHEM*, *622*(1-2), 71-83. https://doi.org/10.1016/S0166-1280(02)00619-X

Nikinmaa, M. (2014). An Introduction to Aquatic Toxicology. In *An Introduction to Aquatic Toxicology*. https://doi.org/10.1016/C2012-0-07948-3

Noman, M. A., Feng, W., Zhu, G., Hossain, M. B., Chen, Y., Zhang, H., & Sun, J. (2022). Bioaccumulation and potential human health risks of metals in commercially important fishes and shellfishes from Hangzhou Bay, China. *Scientific Reports*, *12*(1), 4634. https://doi.org/10.1038/s41598-022-11186-9

Noori, R., Karbassi, A. R., Ashrafi, K., Ardestani, M., & Mehrdadi, N. (2013). Development and application of reduced-order neural network model based on proper orthogonal decomposition for BOD 5 monitoring: Active and online prediction. *Environmental progress & sustainable energy*, *32*(1), 120-127. https://doi.org/10.1002/ep.10611

Noori, R., Karbassi, A., Ashrafi, K., Ardestani, M., Mehrdadi, N., & Nabi Bidhendi, G. R. (2012). Active and online prediction of BOD 5 in river systems using reduced-order support vector machine. *Environmental Earth Sciences*, *67*, 141-149. https://doi.org/10.1007/s12665-011-1487-9

Oo, M. C. M., & Thein, T. (2022). An efficient predictive analytics system for high dimensional big data. *Journal of King Saud University-Computer and Information Sciences*, *34*(1), 1521-1532. https://doi.org/10.1016/j.jksuci.2019.09.001

Ospina, J. D., Zhu, J., Chira, C., Bossi, A., Delobel, J. B., Beckendorf, V., ... & de Crevoisier, R. (2014). Random forests to predict rectal toxicity following prostate cancer radiation therapy. *International Journal of Radiation Oncology* Biology* Physics*, *89*(5), 1024-1031. https://doi.org/10.1016/j.ijrobp.2014.04.027

Pantic, I., Paunovic, J., Cumic, J., Valjarevic, S., Petroianu, G. A., & Corridon, P. R. (2023). Artificial neural networks in contemporary toxicology research. *Chemico-Biological Interactions*, 110269.

https://doi.org/10.1016/j.cbi.2022.110269
Pereira, S., & Tettamanti, M. (2011). Testing times in toxicology-In Vitro vs In Vivo Testing. *Proceedings of Animal Alternatives in Teaching, Toxicity Testing and Medicine. ALTEX Proceedings*, *2*(1), 13.
Polishchuk, P. G., Muratov, E. N., Artemenko, A. G., Kolumbin, O. G., Muratov, N. N., & Kuz'min, V. E. (2009). Application of random forest approach to QSAR prediction of aquatic toxicity. *Journal of chemical information and modeling*, *49*(11), 2481-2488. https://doi.org/10.1021/ci900203n
Rácz, A., Bajusz, D., & Héberger, K. (2019). Intercorrelation limits in molecular descriptor preselection for QSAR/QSPR. *Molecular informatics*, *38*(8-9), 1800154. https://doi.org/10.1002/minf.201800154
Raies, A. B., & Bajic, V. B. (2016). In silico toxicology: computational methods for the prediction of chemical toxicity. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, *6*(2), 147-172. https://doi.org/10.1002/wcms.1240
Rand, G. M., Wells, P. G., & McCarty, L. S. (2020). Introduction to aquatic toxicology. In *Fundamentals of aquatic toxicology* (pp. 3-67). CRC Press. https://doi.org/10.1201/9781003075363-2
Regier, N., Cosio, C., von Moos, N., & Slaveykova, V. I. (2015). Effects of copper-oxide nanoparticles, dissolved copper and ultraviolet radiation on copper bioaccumulation, photosynthesis and oxidative stress in the aquatic macrophyte Elodea nuttallii. *Chemosphere*, *128*, 56-61. https://doi.org/10.1016/j.chemosphere.2014.12.078
Reisfeld, B., & Mayeno, A. N. (2012). *What is computational toxicology?* (pp. 3-7). Humana Press. https://doi.org/10.1007/978-1-62703-50-2_1
Rodríguez-Pérez, R., & Bajorath, J. (2022). Evolution of support vector machine and regression modeling in chemoinformatics and drug discovery. *Journal of Computer-Aided Molecular Design*, *36*(5), 355-362. https://doi.org/10.1007/s10822-022-00442-9
Saha, N., Show, A. K., Das, P., & Nanda, S. (2021). Performance Comparison of Different Kernel Tricks Based on SVM Approach for Parkinson's Disease Detection. In *2021 2nd International Conference for Emerging Technology (INCET)* (pp. 1-4). IEEE. https://doi.org/10.1109/INCET51464.2021.9456233
Saigo, H., Krämer, N., & Tsuda, K. (2008). Partial least squares regression for graph mining. In *Proceedings of the 14th ACM SIGKDD international conference on knowledge discovery and data mining* (pp. 578-586). https://doi.org/10.1145/1401890.1401961
Samim, A. R., Arshad, M., & Vaseem, H. (2022). An insight into various biomarkers to study toxicological impact of nanoparticles in fishes: explored and missing information. *International Journal of Environmental Science and Technology*, 1-20. https://doi.org/10.1007/s13762-022-04488-y
Sarker, I. H. (2021). Machine learning: Algorithms, real-world applications and research directions. *SN computer science*, *2*(3), 160. https://doi.org/10.1007/s42979-021-00592-x
Sattlecker, M., Bessant, C., Smith, J., & Stone, N. (2010). Investigation of support vector machines and Raman spectroscopy for lymph node diagnostics. *Analyst*, *135*(5), 895-901. https://doi.org/10.1039/b920229c
Schmidt, S. N., & Burgess, R. M. (2020). Evaluating polymeric sampling as a tool for predicting the bioaccumulation of polychlorinated biphenyls by fish and shellfish. *Environmental science & technology*, *54*(16), 9729-9741. https://doi.org/10.1021/acs.est.9b07292
Segler, M. H., Kogej, T., Tyrchan, C., & Waller, M. P. (2018). Generating focused molecule libraries for drug discovery with recurrent neural networks. *ACS central science*, *4*(1), 120-131. https://doi.org/10.1021/acscentsci.7b00512
Silva, M. H. (2020). Use of computational toxicology (CompTox) tools to predict in vivo toxicity for risk assessment. *Regulatory Toxicology and Pharmacology*, *116*, 104724. https://doi.org/10.1016/j.yrtph.2020.104724
Silva, M. H., & Kwok, A. (2020). Open access ToxCast/Tox21, toxicological priority index (ToxPi) and integrated chemical environment (ICE) models rank and predict acute pesticide toxicity: a case study. *Int J Toxicol Envr Health*, *5*(1), 102–125.
Silva, M., & Kwok, R. K. H. (2022). Use of computational toxicology tools to predict in vivo endpoints associated with Mode of Action and the endocannabinoid system: A case study with chlorpyrifos, chlorpyrifos-oxon and Δ9Tetrahydrocannabinol. *Current Research in Toxicology*, *3*, 100064. https://doi.org/10.1016/j.crtox.2022.100064
Silver, D., Huang, A., Maddison, C. J., Guez, A., Sifre, L., Van Den Driessche, G., ... & Hassabis, D. (2016). Mastering the game of Go with deep neural networks and tree search. *nature*, *529*(7587), 484-489. https://doi.org/10.1038/nature16961

Singh, A. V., Chandrasekar, V., Paudel, N., Laux, P., Luch, A., Gemmati, D., Tissato, V., Prabhu, K. S., Uddin, S., & Dakua, S. P. (2023). Integrative toxicogenomics: Advancing precision medicine and toxicology through artificial intelligence and OMICs technology. *Biomedicine & Pharmacotherapy*, *163*, 114784. https://doi.org/10.1016/j.biopha.2023.114784

Singh, K. P., Gupta, S., & Basant, N. (2015). QSTR modeling for predicting aquatic toxicity of pharmacological active compounds in multiple test species for regulatory purpose. *Chemosphere*, *120*, 680-689. https://doi.org/10.1016/j.chemosphere.2014.10.025

Singh, K. P., Gupta, S., Basant, N., & Mohan, D. (2014). QSTR modeling for qualitative and quantitative toxicity predictions of diverse chemical pesticides in honey bee for regulatory purposes. *Chemical Research in Toxicology*, *27*(9), 1504-1515. https://doi.org/10.1021/tx500100m

Singh, K. P., Gupta, S., & Rai, P. (2013). Predicting acute aquatic toxicity of structurally diverse chemicals in fish using artificial intelligence approaches. *Ecotoxicology and environmental safety*, *95*, 221-233. https://doi.org/10.1016/j.ecoenv.2013.05.017

Sollazzo, A., Brzozowska, B., Cheng, L., Lundholm, L., Scherthan, H., & Wojcik, A. (2018). Live dynamics of 53BP1 foci following simultaneous induction of clustered and dispersed DNA damage in U2OS cells. *International journal of molecular sciences*, *19*(2), 519. https://doi.org/10.3390/ijms19020519

Souza, T. M., Kleinjans, J. C., & Jennen, D. G. (2019). Toxicogenomics and Toxicoinformatics: Supporting Systems Biology in the Big Data Era. In *Big Data in Predictive Toxicology* (pp. 214-241). https://doi.org/10.1039/9781782623656-00214

Sperotto, A., Molina, J. L., Torresan, S., Critto, A., Pulido-Velazquez, M., & Marcomini, A. (2019). Water quality sustainability evaluation under uncertainty: A multi-scenario analysis based on Bayesian networks. *Sustainability*, *11*(17), 4764. https://doi.org/10.3390/su11174764

Spînu, N., Cronin, M. T., Lao, J., Bal-Price, A., Campia, I., Enoch, S. J., ... & Worth, A. P. (2022). Probabilistic modelling of developmental neurotoxicity based on a simplified adverse outcome pathway network. *Computational Toxicology*, *21*, 100206. https://doi.org/10.1016/j.comtox.2021.100206

Steger-Hartmann, T. (2013). Guest Editorial: Advances in Computational Toxicology. *Molecular Informatics*, *32*(1), 9-9. https://doi.org/10.1002/minf.201380131

Sun, D., Lin, X., Lu, Z., Huang, J., Li, G., & Xu, J. (2022). Process evaluation of urban river replenished with reclaimed water from a wastewater treatment plant based on the risk of algal bloom and comprehensive acute toxicity. *Water Reuse*, *12*(1), 1-10. https://doi.org/10.2166/wrd.2021.023

Sun, L., Zhang, C., Chen, Y., Li, X., Zhuang, S., Li, W., Liu, G., Lee, P. W., & Tang, Y. (2015). In silico prediction of chemical aquatic toxicity with chemical category approaches and substructural alerts. *Toxicology Research*, *4*(2), 452–463. https://doi.org/10.1039/c4tx00174e

Sun, X., Ma, L., Du, X., Feng, J., & Dong, K. (2018, December). Deep convolution neural networks for drug-drug interaction extraction. In *2018 IEEE International conference on bioinformatics and biomedicine (BIBM)* (pp. 1662-1668). IEEE. https://doi.org/10.1109/BIBM.2018.8621405

Svetnik, V., Liaw, A., Tong, C., Culberson, J. C., Sheridan, R. P., & Feuston, B. P. (2003). Random forest: a classification and regression tool for compound classification and QSAR modeling. *Journal of chemical information and computer sciences*, *43*(6), 1947-1958. https://doi.org/10.1021/ci034160g

Swamidass, S. J., Chen, J., Bruand, J., Phung, P., Ralaivola, L., & Baldi, P. (2005). Kernels for small molecules and the prediction of mutagenicity, toxicity and anti-cancer activity. *Bioinformatics*, *21*(suppl_1), i359-i368. https://doi.org/10.1093/bioinformatics/bti1055

Takigawa, I., & Mamitsuka, H. (2013). Graph mining: procedure, application to drug discovery and recent advances. *Drug discovery today*, *18*(1-2), 50-57. https://doi.org/10.1016/j.drudis.2012.07.016

Tan, H., Jin, J., Fang, C., Zhang, Y., Chang, B., Zhang, X., Yu, H., & Shi, W. (2023). Deep Learning in Environmental Toxicology: Current Progress and Open Challenges. *ACS ES&T Water*. https://doi.org/10.1021/acsestwater.3c00152

Tandon, A., Howard, B., Ramaiahgari, S., Maharana, A., Ferguson, S., Shah, R., & Merrick, B. A. (2022). Deep learning image analysis of high-throughput toxicology assay images. *SLAS Discovery*, *27*(1), 29-38. https://doi.org/10.1016/j.slasd.2021.10.014

Tang, X., Zhao, W., & Yu, Q. (2022). Applications of QSAR in Toxicological Risk Assessment of Medical Devices. *Zhongguo yi Liao qi xie za zhi= Chinese Journal of Medical Instrumentation*, *46*(2), 200-205. https://doi.org/10.3969/j.issn.1671-7104.2022.02.018

Tanveer, M., Rajani, T., Rastogi, R., Shao, Y.-H., & Ganaie, M. A. (2022). Comprehensive review

on twin support vector machines. *Annals of Operations Research*, 1–46. https://doi.org/10.1007/s10479-022-04575-w

Tetko, I. V., Klambauer, G., Clevert, D. A., Shah, I., & Benfenati, E. (2022). Artificial intelligence meets toxicology. *Chemical research in toxicology*, *35*(8), 1289-1290. https://doi.org/10.1021/acs.chemrestox.2c00196

Thafar, M. A., Alshahrani, M., Albaradei, S., Gojobori, T., Essack, M., & Gao, X. (2022). Affinity2Vec: drug-target binding affinity prediction through representation learning, graph mining, and machine learning. *Scientific reports*, *12*(1), 4751. https://doi.org/10.1038/s41598-022-08787-9

Todeschini, R., Consonni, V., & Mannhold, R. (2000). Methods and principles in medicinal chemistry. *Kubinyi H, Timmerman H (Series eds) Handbook of molecular descriptors. Wiley-VCH, Weinheim*. https://doi.org/10.1002/9783527628766

Toropova, A. P., Toropov, A. A., Roncaglioni, A., & Benfenati, E. (2023). The System of Self-Consistent Models: QSAR Analysis of Drug-Induced Liver Toxicity. *Toxics*, *11*(5), 419. https://doi.org/10.1002/9783527628766

Trinh, T. X., Seo, M., Yoon, T. H., & Kim, J. (2022). Developing random forest based QSAR models for predicting the mixture toxicity of TiO2 based nano-mixtures to Daphnia magna. *NanoImpact*, *25*, 100383. https://doi.org/10.1016/j.impact.2022.100383

Tropsha, A. (2010). Best practices for QSAR model development, validation, and exploitation. *Molecular informatics*, *29*(6-7), 476-488. https://doi.org/10.1002/minf.201000061

Tugcu, G., Sipahi, H., Charehsaz, M., Aydın, A., & Saçan, M. T. (2023). Computational toxicology of pharmaceuticals. In *Cheminformatics, QSAR and Machine Learning Applications for Novel Drug Development* (pp. 519–537). Elsevier. https://doi.org/10.1016/B978-0-443-18638-7.00007-4

Uesawa, Y. (2016). Rigorous selection of random forest models for identifying compounds that activate toxicity-related pathways. *Frontiers in Environmental Science*, *4*, 9. https://doi.org/10.3389/fenvs.2016.00009

Varghese, A., Agyeman-Badu, G., & Cawley, M. (2020). Deep learning in automated text classification: a case study using toxicological abstracts. *Environment Systems and Decisions*, *40*(4), 465-479. https://doi.org/10.1007/s10669-020-09763-2

Vishwanathan, S. V. N., Schraudolph, N. N., Kondor, R., & Borgwardt, K. M. (2010). Graph kernels. *Journal of Machine Learning Research*, *11*, 1201–1242. https://hdl.handle.net/11858/00-001M-0000-0013-C0B0-C

Vracko, M. (2005). Kohonen artificial neural network and counter propagation neural network in molecular structure-toxicity studies. *Current Computer-Aided Drug Design*, *1*(1), 73-78. https://doi.org/10.2174/1573409052952224

Walker, T. R., & Fequet, L. (2023). Current trends of unsustainable plastic production and micro (nano) plastic pollution. *TrAC Trends in Analytical Chemistry*, 116984. https://doi.org/10.1016/j.trac.2023.116984

Wang, M. W., Goodman, J. M., & Allen, T. E. (2021). Machine learning in predictive toxicology: recent applications and future directions for classification models. *Chemical research in toxicology*, *34*(2), 217-239. https://doi.org/10.1021/acs.chemrestox.0c00316

Wang, Z., & Chen, J. (2019). Background, tasks, modeling methods, and challenges for computational toxicology. *Advances in Computational Toxicology: Methodologies and Applications in Regulatory Science*, 15-36. https://doi.org/10.1007/978-3-030-16443-0_2

Wang, Z., Chen, J., & Hong, H. (2021). Developing QSAR models with defined applicability domains on PPARγ binding affinity using large data sets and machine learning algorithms. *Environmental Science & Technology*, *55*(10), 6857-6866. https://doi.org/10.1021/acs.est.0c07040

Waske, B., van der Linden, S., Benediktsson, J. A., Rabe, A., & Hostert, P. (2010). Sensitivity of support vector machines to random feature selection in classification of hyperspectral data. *IEEE Transactions on Geoscience and Remote Sensing*, *48*(7), 2880-2889. https://doi.org/10.1109/TGRS.2010.2041784

Webb, G. I., Keogh, E., & Miikkulainen, R. (2010). Naïve Bayes. *Encyclopedia of Machine Learning*, *15*(1), 713–714.

Wen, M., Zhang, Z., Niu, S., Sha, H., Yang, R., Yun, Y., & Lu, H. (2017). Deep-learning-based drug–target interaction prediction. *Journal of Proteome Research*, *16*(4), 1401–1409. https://doi.org/10.1021/acs.jproteome.6b00618

Whang, S. E., & Lee, J. G. (2020). Data collection and quality challenges for deep learning. *Proceedings*

of the VLDB Endowment, *13*(12), 3429-3432. https://doi.org/10.14778/3415478.3415562

Wheeler, M. W., Lim, S., House, J. S., Shockley, K. R., Bailer, A. J., Fostel, J., ... & Motsinger-Reif, A. A. (2023). ToxicR: A computational platform in R for computational toxicology and dose–response analyses. *Computational Toxicology*, *25*, 100259. https://doi.org/10.1016/j.comtox.2022.100259

Xu, M., Yang, H., Liu, G., Tang, Y., & Li, W. (2022). In silico prediction of chemical aquatic toxicity by multiple machine learning and deep learning approaches. *Journal of Applied Toxicology*, *42*(11), 1766-1776. https://doi.org/10.1002/jat.4354

Xu, Y., Chou, C.-H., Han, N., Pei, J., & Lai, L. (2023). Graph Kernel Learning for Predictive Toxicity Models. In *Machine Learning and Deep Learning in Computational Toxicology* (pp. 159–182). Springer. https://doi.org/10.1007/978-3-031-20730-3_6

Xue, Y., Li, H., Ung, C. Y., Yap, C. W., & Chen, Y. Z. (2006). Classification of a diverse set of Tetrahymena pyriformis toxicity chemical compounds from molecular descriptors by statistical learning methods. *Chemical research in toxicology*, *19*(8), 1030-1039. https://doi.org/10.1021/tx0600550

Yang, P., Henle, E. A., Fern, X. Z., & Simon, C. M. (2022). Classifying the toxicity of pesticides to honey bees via support vector machines with random walk graph kernels. *The Journal of Chemical Physics*, *157*(3). https://doi.org/10.1063/5.0090573

Yu, X. (2021). Support vector machine-based model for toxicity of organic compounds against fish. *Regulatory Toxicology and Pharmacology*, *123*, 104942. https://doi.org/10.1016/j.yrtph.2021.104942

Yu, X., & Zeng, Q. (2022). Random forest algorithm-based classification model of pesticide aquatic toxicity to fishes. *Aquatic Toxicology*, *251*, 106265. https://doi.org/10.1016/j.aquatox.2022.106265

Yuan, Q., Wei, Z., Guan, X., Jiang, M., Wang, S., Zhang, S., & Li, Z. (2019). Toxicity prediction method based on multi-channel convolutional neural network. *Molecules*, *24*(18), 3383. https://doi.org/10.3390/molecules24183383

Zeidi, A., Rezaei, M. R., Sayadi, M. H., Gholamhosseini, A., & Banaee, M. (2022). Evaluation of polyethylene microplastic bio-accumulation in hepatopancreas, intestine and hemolymph of freshwater crayfish, Astacus leptodactylus. *International Journal of Aquatic Biology*, *10*(4), 273–279. https://doi.org/10.22034/ijab.v10i4.1661

Zeidi, A., Rezaei, M., Sayadi, M. H., Gholamhoseini, A., & Banaee, M. (2023). The effect of microplastics and copper metal on different hemocytes in freshwater crayfish Astacus leptodactylus. *Aquaculture Sciences*, *11*(1), 31–41.

Zhang, H., Ren, J. X., Kang, Y. L., Bo, P., Liang, J. Y., Ding, L., ... & Zhang, J. (2017). Development of novel in silico model for developmental toxicity assessment by using naïve Bayes classifier method. *Reproductive Toxicology*, *71*, 8-15. https://doi.org/10.1016/j.reprotox.2017.04.005

Zhang, Y., Zheng, W., Lin, H., Wang, J., Yang, Z., & Dumontier, M. (2018). Drug–drug interaction extraction via hierarchical RNNs on sequence and shortest dependency paths. *Bioinformatics*, *34*(5), 828-835. https://doi.org/10.1093/bioinformatics/btx659

Zhu, J., Sun, J., Jia, L., Xu, L., Cai, Y., Chen, Y., & Jin, J. (2023). Machine Learning-Enabled Virtual Screening with Multiple Protein Structures toward the Discovery of Novel JAK3 Inhibitors: Integration of Molecular Docking, Pharmacophore, and Naïve Bayesian Classification. *Advanced Theory and Simulations*, 2200835. https://doi.org/10.1002/adts.202200835