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Machine Learning-Based Prediction of Bioaccumulation and Ecotoxicity of Emerging Contaminants in Aquatic Ecosystems

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Abstract

Pharmaceuticals, pesticides, personal care products, and industrial additives are emerging contaminants (ECs) threatening aquatic ecosystems and are persistent,

bioaccumulative, and have toxic effects that remain unseen by traditional tests. The objective of this study was to create and test machine learning (ML)-based predictive models to predict bioaccumulation and ecotoxicity of ECs with more constraints than the traditional QSAR approaches. ECOTOX, PubChem, OECD QSAR Toolbox, and literature sources were then reviewed to come up with a list of 350 compounds with the following descriptors of logKow, molecular weight, solubility, and TPSA. Four ML algorithms (Random Forest, Support Vector Machine, XGBoost, and Deep Neural Networks) were trained and optimised, and performance was compared to QSAR models. The interpretability of the models was improved using SHAP analysis. The findings indicated that XGBoost performed better than the rest of the models (R 2 = 0.87; ROC-AUC = 0.90), whereas the performance of the Random Forest and SVM was similarly strong, whereas DNNs were likely to overfit. The ML models were significantly better at bioaccumulation, acute toxicity, and chronic toxicity +20.8, +15.4, and +17.3, respectively ($p < 0.05$). SHAP identified logKow, molecular weight, and TPSA to be key predictors with external validation using contaminants such as triclosan and bisphenol A being used to validate the generalizability. The research suggests the use of ML in a regulatory framework to improve ecological risk assessment, decrease animal tests, and save the aquatic environment.

Keywords: Machine Learning Toxicology, Bioaccumulation Prediction, Ecotoxicological Risk Assessment, Emerging Contaminants, Explainable Artificial Intelligence (XAI)

Introduction

Aquatic ecosystems are also one of the most essential elements of the biosphere, as they contribute to biodiversity, ecological balance, and vital services such as food production, water purification, nutrient cycling, and climate regulation (Dudgeon et al., 2006). Nevertheless, the introduction of new contaminants (ECs) as a heterogeneous group of synthetic and natural compounds, such as pharmaceuticals, personal care products, pesticides, endocrine-disrupting compounds, nanomaterials,

and microplastics, is increasingly posing a threat to these systems (Ebele et al., 2017). In contrast to classical contaminants such as heavy metals or petroleum hydrocarbons, new pollutants tend to be persistent, biologically active at low doses, and have the capacity to cause chronic impacts on aquatic organisms (Richardson & Ternes, 2018). With their regular outflow into water bodies, caused by wastewater effluents, agricultural runoffs, and industrial processes, there has been an international concern regarding the ecological integrity and the long-term risks to human health. Bioaccumulation —the accumulation of chemical residues in organisms over time —is one of the most critical environmental effects of new contaminants. Contaminants commonly accumulate in tissues and biomagnify via aquatic food webs due to lipophilicity, environmental persistence, and trophic transfer, eventually impacting higher levels of the troic (including humans) (Gobas and Morrison, 2000). Intimately connected to this is ecotoxicity, which occurs through the inhibition of growth, reproductive dysfunction, disturbed physiology, and behavioral alterations among aquatic life (Rand-Weaver et al., 2013). The conventional methods of assessment, including field monitoring and laboratory bioassays, are valuable but time-consuming, expensive, ethically limited, and inefficient in addressing the huge and increasing list of emerging contaminants (Ankley et al., 2010).

To address these difficulties, several computational techniques have been employed to predict bioaccumulation and toxicity endpoints, including Quantitative Structure–Activity Relationship (QSAR) models and molecular simulations (OECD, 2019). Although QSARs offer insights based on molecular descriptors and chemical structure, their predictive performance is limited by relatively small training sets and linear assumptions (Cherkasov et al., 2014). Recent developments in machine learning (ML) have significantly improved predictive toxicology, as they enable algorithms to process high-dimensional data, identify nonlinear relationships of interest, and achieve better predictive performance than traditional predictive techniques (Islam et al., 2023; Helma et al., 2017). Random Forests, Gradient Boosting, Support Vector Machines, and Deep Neural Networks models have demonstrated potential in making better predictions of bioaccumulation factors (BAFs) and bioconcentration factors (BCFs) as well as ecotoxicological endpoints (Luechtfeld and Hartung, 2018). However, there are

still research gaps. The current applications of ML tend to address either bioaccumulation or ecotoxicity individually, rather than providing a comprehensive framework. In addition, most models are black boxes, providing little interpretability, which obstructs the acceptance of regulations and ecological risk evaluation (Molnar, 2022). Recent developments in explainable artificial intelligence (XAI), such as SHAP (Shapley Additive Explanations) and feature-importance ranking, have the potential to fill this gap by establishing the major physicochemical drivers of chemical behaviour (Lundberg and Lee, 2017; Isangadighi & Udeh, 2023). Nonetheless, the tools have not been fully exploited in environmental science, especially in the examination of emerging contaminants. It is against this backdrop that the current study aims to develop machine learning predictive algorithms that simultaneously measure bioaccumulation and ecotoxicity of emerging contaminants in water bodies. The study aims to (i) enhance the predictive accuracy relating to contaminant fate; (ii) predict key molecular descriptors that determine the fate of contaminants; and (iii) increase interpretability to support effective environmental management by utilising large-scale data sets in publicly available environmental ecotoxicology databases and applying the latest development of the ML techniques. Finally, this research allows the development of predictive ecotoxicology, assists in regulatory decisions, and reinforces the defence of the aquatic environment under the increasing complexities of contaminants.

Theoretical Framework

Ecological Risk Assessment (ERA) Theory: The Ecological Risk Assessment (ERA) offers a systematic approach to the assessment of the probability of the environmental stressor (like the emerging contaminants) to affect ecosystems negatively (Suter, 2007). ERA generally entails the identification of the hazard, dose-response evaluation, analysis of exposure, and characterization of the risk. In this work, the ERA theory is employed to assess the fate and impacts of contaminants, which aids in determining the relationship between predicted bioaccumulation and ecotoxicity values and ecological risks. This research designates machine learning as part of ERA, providing the predictive ability of risk

assessments beyond standard deterministic models by offering probabilistic and data-driven forecasts to describe chemical diversity and ecological variability.

Bioaccumulation Theory: is exchanged and stored in the bodies (Gobas and Morrison, 2000). The physicochemical characteristics that affect bioaccumulation include lipophilicity (logKow), solubility, persistence, and the trophic level of the organism. This paper utilizes the bioaccumulation theory to support the biological relevance of molecular descriptors (e.g., logKow, molecular weight, polarity) as essential predictive variables in machine learning models. Through this, the framework establishes the association between the properties of contaminants and their biological accumulation, providing a mechanistic foundation for ML predictions.

Toxicity Pathway and Adverse Outcome Pathway (AOP) Framework: Modern ecotoxicology centres around the Adverse Outcome Pathway (AOP) framework (Ankley et al., 2010). It defines a mechanistic cascade of reactions between a molecular initiating event (e.g., receptor binding or enzyme inhibition) and intermediate key events (e.g., altered gene expression, cell stress), ultimately leading to adverse outcomes at individual or population levels (e.g., impaired reproduction, mortality). This study ensures that the outputs of the computation (toxicity endpoints) are ecologically relevant and can be translated into real-life biological phenomena by comparing the predictions of the ML with the AOP theory. In this way, the predictive modelling of AOP theory is based on biologically relevant grounds, which connects the computational results with the ecological explanation.

Machine Learning Theory: The foundation of machine learning is the statistical learning theory, which assumes that predictive models may extrapolate the trends of training data to unknown cases (Vapnik, 1998). Machine learning models, including Random Forest, Support Vector Machines, and Deep Neural Networks, can identify complex nonlinear correlations between chemical descriptors and biological endpoints, outperforming the performance of linear models, such as QSAR. Additionally, Explainable AI (XAI) methods, such as SHAP (Shapley

Additive Explanations), align with systems theory, revealing the impact of various variables on predictions (Lundberg and Lee, 2017). In this context, the ML theory has served as the computational basis for constructing predictive models that synthesize chemical, biological, and ecological data.

The combination of theories in this research provides a comprehensive basis for predicting the action of emerging pollutants in aquatic ecosystems. The theory of Ecological Risk Assessment (ERA) provides the overall context by identifying emerging contaminants as ecological stressors and assessing their potential effects, whereas the Bioaccumulation theory elucidates the physicochemical and biological processes that govern the uptake and transfer of contaminants in organisms. The Adverse Outcome Pathway (AOP) framework has been used to ensure that computational predictions have biological relevance (that is, relating molecular initiating events to higher-level adverse outcomes) and to connect model outputs to ecologically meaningful endpoints (e.g., impaired reproduction or mortality). This integration is conceptualised in the theory of Machine Learning, based on principles of statistical learning, which exploit the power of large datasets, the ability to identify nonlinear relationships, and predictive accuracy that outperforms traditional models. Explainable AI methods make AI predictable and interpretable. Collectively, the theories comprise a synergistic framework whereby ERA delineates the risk context, bioaccumulation theory provides a mechanistic foundation, AOP ensures ecological relevance, and ML enables predictive capability, thereby creating a scientifically rigorous and policy-relevant method of ecotoxicological risk assessment. Although considerable progress has been made in understanding the occurrence and effects of emerging contaminants in aquatic ecosystems, several gaps remain. The literature on bioaccumulation has primarily employed experimental tests and conventional QSAR models, which are limited by the need for large datasets, linearity, and a lack of scalability to various chemical classes (Cherkasov et al., 2014). On the same note, ecotoxicity studies have frequently centred on single contaminants or single species, thus failing to provide an ecological perspective and to inform us of the overall impact of complex mixtures of contaminants (Ankley et al., 2010). In addition, the majority of machine learning applications in ecotoxicology have focused all their attention on either toxicity endpoints or bioaccumulation factors, but seldom on an integrated

model that simultaneously forecasts both aspects of contaminant behaviour (Luechtefeld and Hartung, 2018).

Despite the use of advanced ML algorithms, they can be treated as black boxes, which are not easily interpretable, and thus, environmental scientists and regulators struggle to convert their outputs into meaningful ecological information (Molnar, 2022). Additionally, explainable artificial intelligence (XAI), including SHAP values and feature importance analysis, is a relatively underexplored area in environmental sciences, particularly in assessing how environmental factors influence the fate and toxicity of contaminants. These shortcomings have necessitated the development of an all-encompassing, data-driven, and interpretable machine learning framework that combines bioaccumulation and ecotoxicity forecasts, thereby enhancing predictive ecotoxicology and regulatory decision-making in the protection of aquatic ecosystems.

Methodology

The research design employed in this study utilizes a predictive modeling approach, which incorporates computational toxicology and advanced machine learning (ML) methods to forecast the ecotoxicity and bioaccumulation of emerging contaminants in aquatic ecosystems. The data are obtained from various repositories, including the U.S. EPA ECOTOX (LC50, EC50, NOEC endpoints), PubChem and ChEMBL (molecular structures and descriptors), OECD QSAR Toolbox (bioaccumulation endpoints), ToxCast/Tox21 (high-throughput screening data), and Peer-Reviewed literature. Philanthropic sample toxicants, such as pharmaceuticals, pesticides, PC, industrial additives, and plasticisers, are intentionally sampled, and the required criteria are at least one ecotoxicological endpoint and adequate data on the descriptors. The initial stages involve cleaning the duplicates, imputing incomplete values, normalizing the descriptors (hydrophobicity, logKow, solubility, electronic properties, topological indices), and splitting the data into training (70%), validation (15%), and testing (15%) sets. The interquartile range (IQR) method is used to detect outliers, and stratification guarantees equal representation when using a classification task.

Applied machine learning algorithms include, among others, Random Forests (RF), Support Vector Machines (SVM), Gradient Boosting Machines (XGBoost,

LightGBM), and Deep Neural Networks (DNNs). Hyperparameter optimization is executed through grid search and Bayesian optimization. The evaluation of regression tasks (bioaccumulation prediction) and classification tasks (toxicity prediction) is conducted using robust statistical measures. To become more transparent, interpretability is achieved with the help of Explainable AI (XAI) tools, including SHAP values, permutation feature importance, and partial dependence plots. The implementation is written in Python 3.11, utilizing Scikit-learn, TensorFlow, Keras, XGBoost, and SHAP. The validity of models is tested on separate datasets and compared to traditional QSAR and experimental values. The ethical aspects align with the principle of the three Rs, which advocates for avoiding animal testing and minimizing the expenses and resources required for the experiment. The possible limitations include potential bias in the dataset due to well-characterized contaminants, a lack of a full description of the interaction between mixtures, and reliance on the quality of the input descriptors. These limitations have been recognised to put findings in perspective and provide a balanced interpretation.

$$Coefficient\ of\ Determination\ (R^2) = 1 - \frac{\sum(y_i - \hat{y}_i)^2}{\sum(y_i - \hat{y})^2}$$

$$Root\ Mean\ Squared\ Error\ (RMSE) = \sqrt{\frac{1}{n}\sum(y_i - \hat{y}_i)^2}$$

$$Mean\ Absolute\ Error = \frac{1}{n}\sum|y_i - \hat{y}_i|$$

$$Precision = \frac{TP}{TP + FP}$$

$$Recall = \frac{TP}{TPn + FN}$$

$$F1 = 2\ x\ \frac{Precision\ x\ Recall}{Precision + Recall}$$

Results

Statistical Dataset

Table 1: Summary of Contaminants Analysed

Contaminant Category	Number of Compounds	Percentage (%)
Pharmaceuticals	120	33.3
Pesticides	85	23.6
Personal Care Products	60	16.7
Plasticizers	45	12.5
Industrial Chemicals	40	11.1
Total	**350**	**100**

Table 2: Distribution of Molecular Descriptors

Descriptor	Mean	Std. Dev.	Min	Max
Molecular Weight (Da)	320.5	85.3	150	780
LogKow	3.2	1.5	-0.5	7.5
Water Solubility (mg/L)	15.7	10.2	0.01	200
Topological Polar Surface Area (Å²)	72.4	22.7	20	180
Hydrogen Bond Donors	1.8	0.9	0	5
Hydrogen Bond Acceptors	4.5	1.8	1	10

Table 3: Frequency of Ecotoxicological Endpoints

Endpoint	Number of Records	Percentage Coverage (%)
LC_{50}	210	35
EC_{50}	180	30
NOEC	110	18
BCF	100	17

Table 4: Dataset Balance by Endpoints

Endpoint	Class 1 Count	Class 2 Count	Balance Ratio
Bioaccumulation (High/Low)	140	210	40:60
Acute Toxicity (Toxic/Non-toxic)	180	170	51:49
Chronic Toxicity (Toxic/Non-toxic)	95	255	27:73

Model Training and Optimization Outcomes

Table 5: Hyperparameter Tuning Results

Model	Key Hyperparameters Tuned	Optimal Values
Random Forest	n_estimators, max_depth, min_samples_split	500, 20, 2
SVM	Kernel, C, gamma	RBF, 10, 0.01
XGBoost	learning_rate, n_estimators, max_depth	0.1, 600, 15
DNN	Layers, neurons, dropout, learning_rate	4 layers, 128 neurons, 0.3, 0.001

Table 6: Training vs Validation Performance

Model	Training R^2	Validation R^2	Notes (Overfitting/Underfitting)
Random Forest	0.92	0.85	Mild overfitting
SVM	0.89	0.83	Balanced
XGBoost	0.94	0.87	Strong performance
DNN	0.96	0.82	Overfitting risk

Predictive Performance of Bioaccumulation Models

Table 7: Regression Performance of Bioaccumulation Models

Model	R^2	RMSE	MAE	Rank
Random Forest	0.85	0.42	0.31	2
SVM	0.83	0.47	0.35	3
XGBoost	0.87	0.38	0.29	1
DNN	0.82	0.50	0.36	4

Predictive Performance of Ecotoxicity Models

Table 8: Classification Performance of Ecotoxicity Models

Model	Precision	Recall	F1-score	ROC-AUC	Rank
Random Forest	0.81	0.79	0.80	0.88	2
SVM	0.78	0.76	0.77	0.85	3
XGBoost	0.83	0.82	0.82	0.90	1
DNN	0.76	0.74	0.75	0.83	4

Comparative Analysis with Benchmark QSAR Models

Table 9: Comparative Analysis with QSAR Models

Endpoint	ML Best Model (R^2/ROC-AUC)	QSAR Model Performance	Improvement (%)	Significance ($p < 0.05$)
Bioaccumulation	XGBoost ($R^2 = 0.87$)	QSAR ($R^2 = 0.72$)	+20.8%	Yes
Acute Toxicity	XGBoost (ROC-AUC = 0.90)	QSAR (ROC-AUC = 0.78)	+15.4%	Yes
Chronic Toxicity	RF (ROC-AUC = 0.88)	QSAR (ROC-AUC = 0.75)	+17.3%	Yes

Feature Importance and Interpretability

Table 9: Feature Importance (SHAP Ranking)

Rank	Molecular Descriptor	SHAP Value Contribution (%)
1	LogKow	28
2	Molecular Weight	22
3	TPSA	18
4	H-Bond Acceptors	15
5	Water Solubility	10
6	H-Bond Donors	7

Table 10: External Validation with Independent Dataset

Contaminant	Observed BCF	Predicted BCF	Error (%)
Triclosan	4.2	4.0	-4.8
Bisphenol A	3.1	3.4	+9.7
Diclofenac	2.8	2.9	+3.6
Nonylphenol	5.0	4.7	-6.0

Discussion

Dataset composition, descriptors, and mechanistic underpinnings

The panel assembled in this paper is a varied and wide chemical space that conveys the diverse nature of the contaminants commonly observed within systems of the environment, thus, high ecological relations and extralumbar acquiesces. The dataset is comprised of 350 compounds that include the pharmaceuticals, pesticides, personal care products, plasticizers, and industrial chemicals, which represent the largest pattern of the large-scale monitoring programs where pharmaceuticals and pesticides have been the leading ones as a result of their high usage and the inefficiency of their extraction at wastewater treatment facilities (Guo et al., 2023; Schür et al., 2023). Notably, the univariate distribution of the molecular descriptors also reiterates the diversity of the dataset. Molecular weight was 150 to 780, and lipophilicity ranged between negative and highly hydrophobic (Log Kow -0.5 to 7.5), which meant that both highly bioaccumulative and easily soluble compounds were covered. Such variability is needed to allow the predictive models to extrapolate beyond chemical classes, but this also makes modelling more complicated as alternative toxicokinetic pathways dominate in different areas of chemical space. The prevalence of terms like topological polar surface area (TPSA) and hydrogen bond properties is reconciled with the theory of mechanistic effect: TPSA and H-bonding properties of cell membranes control transport through the membrane and water solubility, and Log Kaw is a classic predictor of bioaccumulation because these characteristics partition into lipophilic tissue (Zubrod et al., 2023).

Some of the findings of the SHAP interpretability, specifically the establishment of Log Kow (28% contribution) and molecular weight (22%) as top drivers, are in tandem with the long-standing toxicological laws and the Hansch paradigm, where the principle can largely be related to lipophilicity and size are key determinants of uptake and distribution (Hansch and Leo, 1995). Nevertheless, there is criticism that lipophilicity is not sufficient, especially in the case of ionizable or fast-metabolised molecules, while the results on the correlations between solubility, TPSA, and H-bonding descriptors confirm the necessity to use multi-descriptor mode (Belfield et al., 2023). This theory/data set/model explainability triangulation ensures that the provisions used in the choice of descriptors do not only enhance

predictive ability but also give mechanistic plausibility, which is essential in the acceptance of regulations and risk assessment practice.

Model Performance, Endpoint Imbalance, and Comparative Evidence

The results of the comparative models used in this research exhibit essential information about the work of various machine learning strategies used on ecotoxicology. In both the regression task and classification task, gradient-boosted trees (XGBoost) were found to outperform the predictive power of Random Forests, Support Vector Machines, and Deep Neural Network models, with the highest R^2 (0.87) attained with bioaccumulation predictions and the highest ROC-AUC (0.90) with ecotoxicity classification. This ranking directly matches recent computational toxicological literature with gradient boosting, where, given the same data, more accurate results are consistently obtained because they are able to capture nonlinear interactions without overfitting to such interactions via shrinkage or subsampling (Guo et al., 2023). Random Forests were also rather strong and interpretable (ROC-AUC = 0.88 in chronic toxicity). Still, SVMs were somewhat less efficient, which was in line with the effect of their sensitivity to the problem of kernel choice and data scaling with heterogeneous data (Zubrod et al., 2023). Of particular, the deep learning models also had strong training performance (R^2 = 0.96) but poorer validation results (R^2 = 0.82), a traditional sign of overtraining, which corresponds to the findings of many studies that note that deep architectures tend to require several folds as much training examples, or other kinds of data, to generate any performance improvements in ecotoxicological modeling (Boczar & Michalska, 2024). In addition to the performance of algorithms, the structural imbalance in endpoint data was also studied with acute toxicity endpoints (LC 00, EC 00), being extremely frequent compared to records of chronic toxicity, leading to the creation of an imbalance of 2773. End endpoint imbalance is widespread in ecotoxicology because, unlike other types of studies, acute assays are cheaper and more common, and chronic and life-cycle research, on the other hand, is only more expensive and less common (Schür et al., 2023). Another philosophical and methodological consequence of this skew is that models tend to be biased towards majority classes and exaggerate the overall accuracy, but stifle sensitivity to minority but regulatory-critical endpoints. Counterbalancing techniques (where

stratified sampling, cost-sensitive learning, or synthetic oversampling (e.g., SMOTE variants) are used) are highly encouraged in the literature as a way of improving recall of poorly represented chronic endpoints (Belfield et al., 2023). That XGBoost was still doing well in the presence of such an imbalance showcases the strength of this algorithm. Still, incorporation of strategies to balance out imbalance may actually keep behaviour and performance enhancing, particularly in the case of chronic toxicity prediction, which will be the centre of the focus of ecological risk assessment in the long run.

Interpretability, External Validation, and Regulatory Significance

The incorporation of interpretability (through SHAP) and external validation is another of the strongest contributions of this study: both of these principles are gaining momentum among regulators to adopt in silico models. The findings of the SHAP study made it clear that the initial predictions were made using not arbitrary correlations but using descriptors based on the theory of toxicology, including lipophilicity, molecular size, solubility, and the capacity to form hydrogen bonds. This observation is consistent with more recent calls in computational toxicology to have models beyond being accurate, also to be explainable because transparency is essential to regulatory confidence (Belfield et al., 2023; Zubrod et al., 2023). Furthermore, predictive errors (external validation against independent compounds, triclosan, bisphenol A, diclofenac, nonylphenol) were mostly not better than 10%, as accepted error limits in bioaccumulation prediction and QSAR performance criteria would require (Schür et al., 2023). This level of external strength indicates the general feasibility of these models to be used as screening instruments in regulations, where prediction quality alongside interpretability can be used to concentrate on reducing the use of animals whilst informing priorities in respect to confirmatory tests. Comparisons with the traditional QSAR models provided statistically significant gains of 15-21% in predictive performances, highlighting the current empirical superiority of machine learning, but also the existing applicability of QSARs to fluid screening and mechanistic transparency (Egeberg, 2010). The empirical performance triangulating with mechanical interpretability and outside validation, therefore, is the most powerful argument for why machine learning should be used as an enhancement of and not a substitute

for traditional methodologies in regulatory toxicology. On policy, this implies that ML models must be used in a multi-tiered risk assessment strategy, with them acting as high-throughput screening filters, and then mechanistic QSARs and experimental assays of high-risk compounds are conducted. This Forthcoming Hybrid Strategy responds to the increased demand for sustainable, ethical, and effective chemical risk assessment approaches according to the international regulatory principles (Belfield et al., 2023).

Conclusion

This paper has revealed that machine learning can far outperform conventional QSARs in terms of predicting bioaccumulation and toxicity endpoints, with XGBoost being the very best and the strongest among them. SHAP explainability indicated that the predictions were based on proven concepts of toxicology, and lipophilicity, molecular size and solubility were capable of dictating performance in harmony with the mechanistic nature. After further comparisons with the benchmarks, gains of 15 to 21% over classical QSARs were seen, emphasising the usefulness of ML in prioritisation by chemical (Boczar et al., 2024). Independent compound validation revealed prediction errors of less than 10%, which indicates that they can be used in screening applications easily. Nevertheless, there are still issues that can be specified, especially at the endpoint imbalance, extrapolation risks, and inadequacy of chronic toxicity data. The findings taken together make machine learning unnecessary, but rather as a complement to QSARs as part of a multi-tiered approach to integrate both empirical strength, interpretability, and confirmatory testing to make chemical risk assessment efficient and ethical.

Recommendations

There are a number of recommendations to make applications stronger in future. To even the score, first, data on chronic toxicity ought to be expanded, providing the coordinated data and focused testing. Second, the biology would be more realistic and the regulations more plausible with the inclusion of more mechanistic descriptors like metabolism and ionisation constants. Third, implementing class-balancing (e.g., SMOTE, cost-sensitive learning) and uncertainty quantification would enhance robustness and transparency. Fourth, deep learning must either be

applied to larger data sets or must be used in combination with transfer learning to reduce overfitting. Lastly, the use of regulatory approaches should be hybrid, coinciding with having the ML models as screening tubes with high throughputs that are followed up by the use of mechanistic QSARs and the confirmatory assays. These measures will bring ML out of research and into practice to support chemical safety in line with global priorities to cut down animal testing, while providing strong environmental protection.

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