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IN SILICO TOXICITY SCREENING: FROM CONVENTIONAL TO DIGITAL TOXICOLOGY

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ABSTRACT

Toxicity remains a major consideration in drug discovery because a compound must combine therapeutic activity with an acceptable safety profile. Conventional toxicity testing provides essential biological evidence but can be resource-intensive and may be difficult to apply to large chemical libraries at an early stage. In silico toxicity screening provides a complementary, data-driven approach for identifying potential safety liabilities before extensive experimental testing. This review summarises the transition from conventional toxicology to digital toxicology and discusses quantitative structure–activity relationship (QSAR) modelling, read-across, molecular docking, toxicokinetic modelling, machine learning, deep learning and artificial intelligence (AI) approaches. Major toxicity endpoints, including cardiotoxicity, hepatotoxicity, nephrotoxicity, neurotoxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, immunotoxicity and respiratory toxicity, are considered from a computational perspective. The article also examines how computational methods can support ADMET profiling, lead optimisation, candidate prioritisation and early toxicity-based deprioritisation. Although digital methods can improve speed, scalability and consistency, their reliability depends on data quality, model validation, applicability domain, interpretability and

experimental confirmation. Future toxicology is expected to increasingly integrate AI, multi-omics, human-relevant in vitro systems, organ-on-chip models and New Approach Methodologies (NAMs). Overall, computational toxicity assessment is best viewed as a complementary component of an integrated safety strategy rather than a replacement for experimental toxicology.

KEYWORDS: in silico toxicology; toxicity screening; QSAR; read-across; machine learning; artificial intelligence; ADMET; drug discovery; computational toxicology.

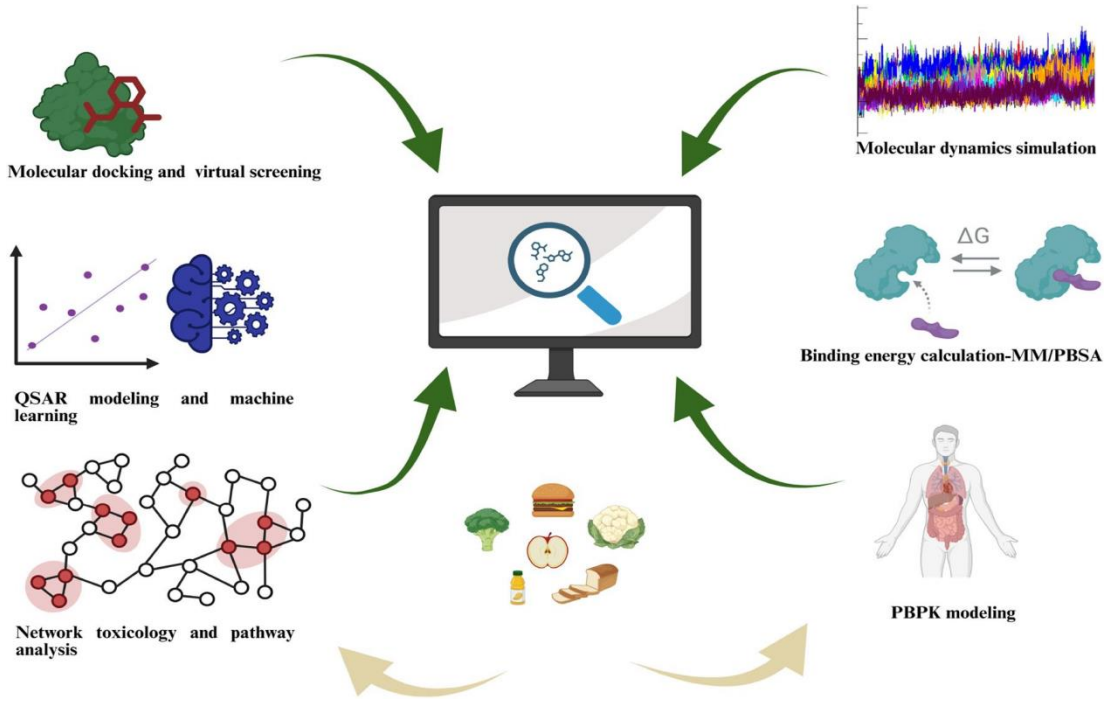
1. INTRODUCTION

Drug discovery and development is a complex and time-consuming process in which the identification of safe and effective therapeutic compounds remains a major challenge. A potential drug candidate must demonstrate sufficient pharmacological activity along with an acceptable safety profile. Toxicity is one of the important factors responsible for failure during drug development; therefore, early identification of toxicological risks is essential for improving the efficiency and success of the drug discovery process.[1] Traditionally, drug toxicity has been assessed using a combination of in vitro laboratory experiments and in vivo animal studies. Although these approaches provide valuable information, they are often expensive, time-consuming, labor-intensive, and require considerable quantities of test compounds.[2]

The limitations associated with conventional toxicity testing have encouraged the development of computational approaches for predicting the safety of chemical compounds. In silico toxicity screening refers to the use of computer-based methods, mathematical models, chemical structures, biological information, and computational algorithms to predict the potential toxic effects of drugs and other chemical substances.[3] These approaches can be applied during the early stages of drug discovery to identify compounds that may possess undesirable toxicological properties before extensive experimental testing is performed. Consequently, computational toxicology has become an important component of modern drug safety assessment.

One of the most established computational approaches is quantitative structure–activity relationship (QSAR) modeling, which establishes mathematical relationships between chemical structure and biological or toxicological activity. QSAR models use molecular descriptors such as molecular weight, hydrophobicity, electronic properties, topological

characteristics, and structural fragments to predict the toxicity of unknown compounds.[4] QSAR-based methods have been used to predict several toxicological endpoints, including acute toxicity, mutagenicity, carcinogenicity, hepatotoxicity, reproductive toxicity, and developmental toxicity. These predictions can help researchers identify potentially hazardous compounds and modify their chemical structures during the lead optimization stage.



Another important approach is **read-across**, in which toxicity information from structurally or biologically similar compounds is used to estimate the toxicity of a compound for which experimental data are unavailable or limited.[5] Toxicological databases containing chemical structures, experimental toxicity data, biological activities, and mechanistic information provide valuable resources for computational safety assessment. Chemical similarity and structural-alert approaches can also identify specific molecular features that have previously been associated with toxicological effects. By combining these approaches, researchers can obtain useful preliminary information about the possible safety profile of a new chemical entity.

Recent advances in **artificial intelligence (AI) and machine learning (ML)** have further transformed computational toxicology. Machine learning algorithms can identify complex relationships between molecular characteristics and toxicity outcomes using large datasets. Algorithms such as random forests, support vector machines, artificial neural networks, gradient boosting, and deep learning have been increasingly applied for toxicity prediction.[6]

These approaches can analyze large numbers of compounds and multiple molecular features, thereby supporting rapid screening of chemical libraries. Deep learning methods, including graph-based neural networks, can directly utilize molecular structures and identify complex structural patterns associated with toxicological activity.

In silico toxicity screening can also be integrated with **ADMET prediction**, which evaluates absorption, distribution, metabolism, excretion, and toxicity properties of drug candidates. A compound may have strong therapeutic activity but still fail because of poor pharmacokinetic characteristics or unacceptable toxicity. Therefore, simultaneous evaluation of ADMET properties during early drug discovery can help researchers prioritize compounds with more suitable overall profiles.[1, 3] Computational prediction of hepatotoxicity, cardiotoxicity, nephrotoxicity, genotoxicity, and other organ-specific toxicities can provide additional information for evaluating potential safety concerns.

An important advantage of computational toxicology is its potential to support the **3Rs principle—Replacement, Reduction, and Refinement** of animal experimentation. Although computational methods cannot completely replace experimental toxicity studies, they can help reduce the number of compounds that require extensive laboratory testing by prioritizing candidates according to their predicted safety profiles.[2,5] Compounds predicted to have significant toxicity can be eliminated or structurally modified at an early stage, while promising compounds can be selected for further experimental evaluation. Thus, in silico screening can complement conventional toxicological studies and improve the efficiency of the drug development process.

Despite its advantages, computational toxicity prediction has certain limitations. The reliability of a prediction depends strongly on the quality, quantity, and diversity of the data used for model development.[4,6] Models trained using limited or biased datasets may produce inaccurate predictions when applied to structurally different compounds. Therefore, proper model validation, applicability-domain assessment, and consideration of prediction uncertainty are essential. Computational predictions should generally be interpreted together with experimental and mechanistic evidence rather than being considered as complete replacements for laboratory studies.

Overall, **in silico toxicity screening is transforming drug safety assessment by enabling rapid, cost-effective, and systematic identification of potential toxicological risks during**

the early stages of drug development. The integration of QSAR modeling, read-across, ADMET prediction, machine learning, deep learning, and toxicological databases provides a powerful framework for modern computational toxicology.[3,6] When combined appropriately with in vitro and in vivo evidence, these computational approaches can support safer drug design, reduce unnecessary experimental testing, identify potential toxicity at an early stage, and improve the efficiency of the drug discovery process. Continued development and validation of computational methods is therefore expected to play an increasingly important role in the future of drug safety assessment.[7,8]

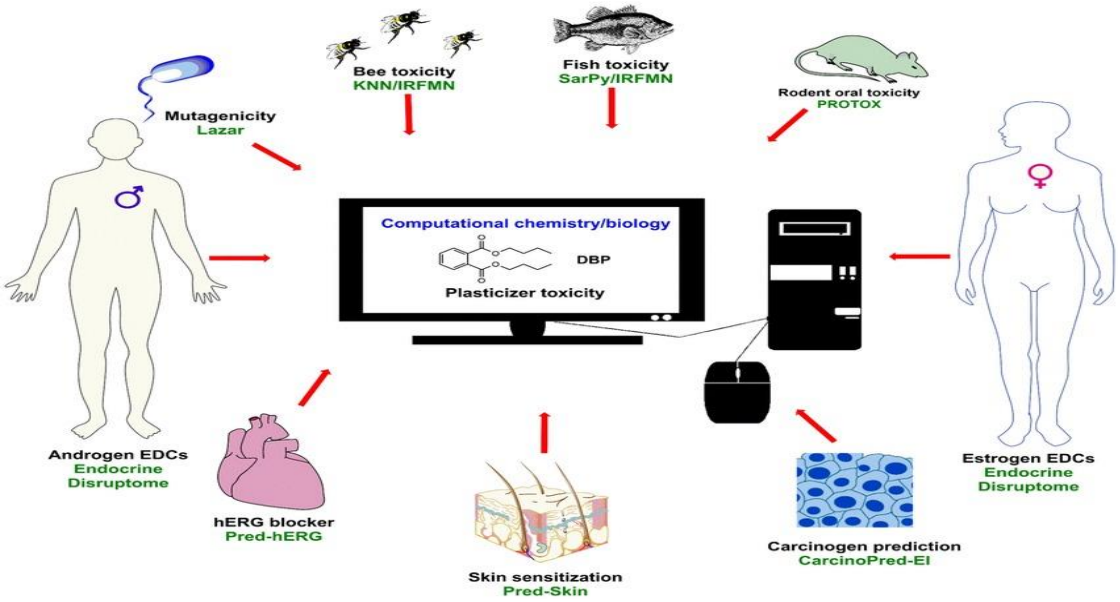
3. From Conventional Toxicology to Digital Toxicology

Conventional toxicology has traditionally relied on **in vivo animal studies, in vitro experiments, biochemical assays, and histopathological evaluation** to determine the potential hazards associated with chemicals and drugs. These approaches have played a fundamental role in understanding toxicity; however, they can be time-consuming, expensive, and dependent on large amounts of experimental data. In addition, conventional approaches may have limitations when toxicity information is unavailable for newly developed or poorly characterized chemicals.[3,9] These challenges have encouraged the development of alternative and complementary approaches collectively referred to as **New Approach Methodologies (NAMs)**, which include in vitro, in silico, omics-based, and computational methods.[10]

The transition toward **digital toxicology** represents a shift from predominantly experimental testing to a data-driven approach in which computational models, chemical databases, high-throughput screening, artificial intelligence (AI), and machine learning (ML) are integrated into toxicological assessment. In silico methods such as **Quantitative Structure–Activity Relationship (QSAR), read-across, molecular docking, molecular similarity analysis, and machine-learning models** can be used to predict potential toxic effects from chemical structure and previously available biological data.[3,11] QSAR models, for example, establish relationships between molecular descriptors and biological or toxicological endpoints, allowing toxicity to be estimated for chemicals for which experimental information may be limited.

Read-across is another important computational approach. In this method, toxicity information from a structurally or mechanistically similar chemical is used to provide information about a data-poor chemical. Similarity can be assessed using molecular structure,

physicochemical properties, metabolic characteristics, or biological activity.[3, 12] Although read-across can help fill toxicological data gaps, the reliability of the prediction depends on the quality of the available data and the biological relevance of the selected analogue.



The emergence of **artificial intelligence and machine learning** has further expanded the capabilities of digital toxicology. Large datasets generated from high-throughput screening programs can be analyzed to identify complex relationships between chemical structures, biological targets, molecular pathways, and adverse outcomes. Modern computational approaches can integrate multiple data types, including chemical descriptors, transcriptomics, proteomics, metabolomics, and other omics data, to support toxicity prediction.[11, 13] However, AI-based predictions require appropriate training data, validation, interpretation, and assessment of uncertainty before they can be considered reliable for toxicological decision-making.

An important concept in this transition is the **Adverse Outcome Pathway (AOP)** framework, which connects an initial molecular interaction with subsequent cellular, tissue, organ, and organism-level changes leading to an adverse outcome. Integration of computational predictions with AOP knowledge can provide a mechanistic basis for interpreting toxicity rather than relying only on statistical correlations.[11] Regulatory organizations such as the OECD are also supporting the development and evaluation of NAMs, including computational and in vitro approaches, as part of modern chemical safety assessment.[10]

Thus, digital toxicology does not necessarily replace conventional toxicology; rather, it **complements experimental approaches by improving prediction, prioritization, data integration, and toxicological decision-making**. The overall transition can therefore be viewed as a progression from individual laboratory experiments toward an integrated system combining experimental data, computational modelling, high-throughput screening, AI/ML, and mechanistic toxicology. Recent developments also indicate increasing interest in AI-assisted read-across and computational approaches for addressing toxicological data gaps.[14]

Evolution from Conventional Toxicology to Digital Toxicology

Target Chemical & Endpoint Definition

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Source Chemical Selection

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Chemical Similarity Assessment

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Toxicological Data Evaluation

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Read-Across Hypothesis

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Weight of Evidence & Uncertainty Assessment

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Regulatory/Scientific Conclusion

4. Decoding In Silico Toxicity Screening

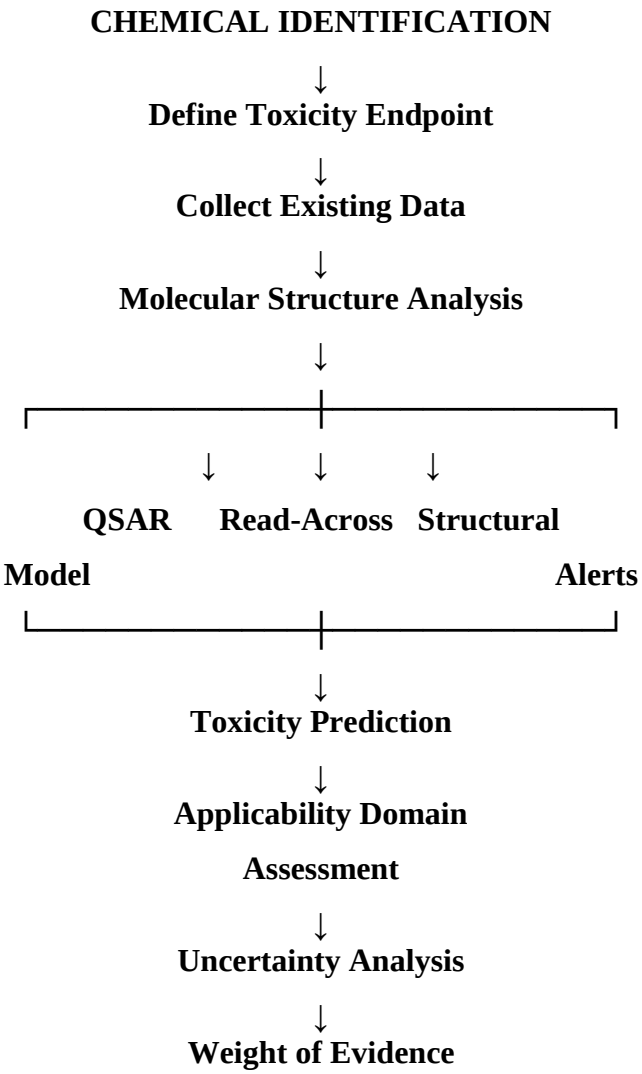
Introduction

In silico toxicity screening is a computer-based approach used to predict the potential toxic effects of chemicals by using their molecular structure, physicochemical properties, biological activity and previously available toxicological data. It is an important component of modern computational toxicology because it can provide rapid information about potential hazards and help prioritize chemicals for further experimental testing. Common approaches include **Quantitative Structure–Activity Relationship (QSAR), read-across, structural alerts, molecular docking, machine learning and mechanistic approaches based on Adverse Outcome Pathways (AOPs)**.

The fundamental principle is that **chemical structure and biological activity are related**. Therefore, chemicals with similar structural or biological characteristics may show similar toxicological behaviour. QSAR models establish relationships between molecular descriptors and toxicity endpoints, whereas read-across uses toxicity information from similar chemicals with known experimental data. Structural alerts identify chemical substructures that are associated with particular toxicological effects.

Principle and Workflow

The general workflow of in silico toxicity screening begins with **chemical identification and endpoint selection**. The molecular structure of the target chemical is then analysed and relevant experimental and computational data are collected. Depending on the endpoint, appropriate methods such as QSAR, structural alerts or read-across are selected. The generated prediction is subsequently evaluated for **applicability domain, reliability and uncertainty** before being integrated with other available evidence.

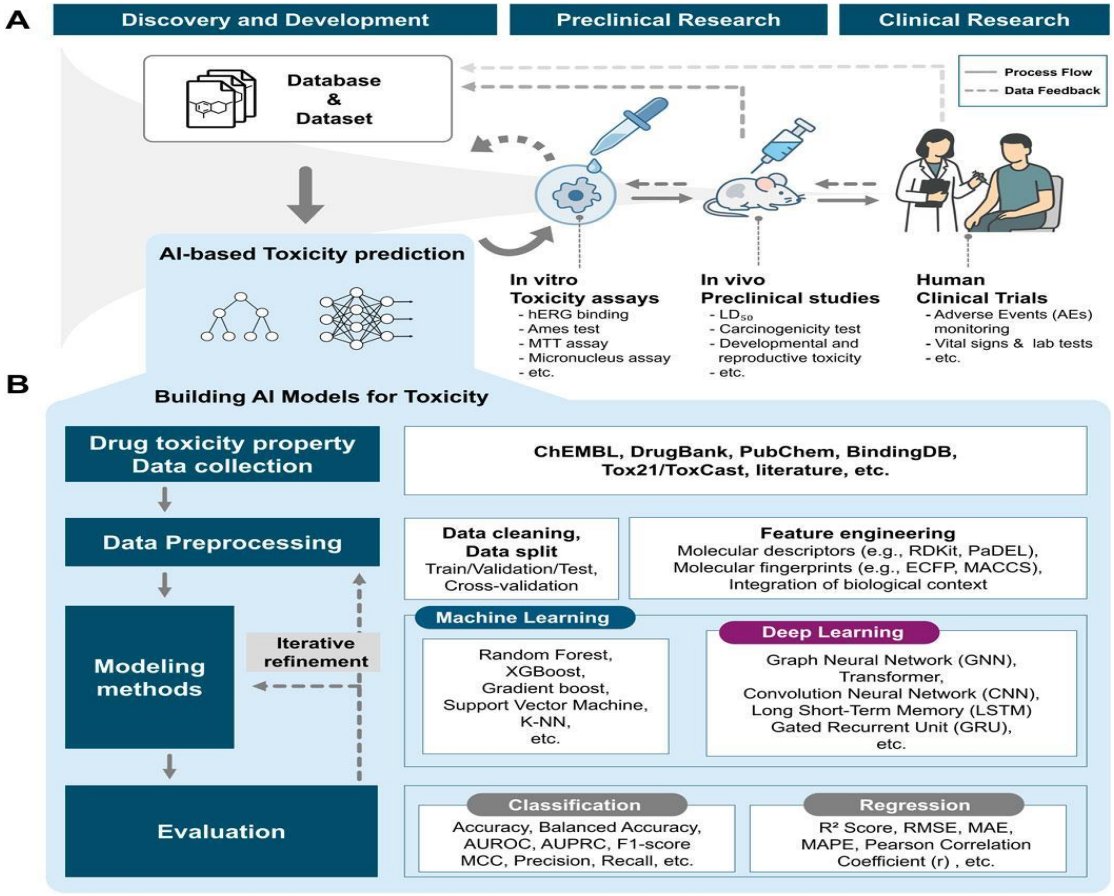


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Further Testing if Needed

4.1. General workflow of in silico toxicity screening.

However, computational predictions should not be interpreted independently of their **data quality, model performance, applicability domain and uncertainty**. Structural alerts may not capture all possible mechanisms of toxicity, while read-across depends strongly on the selection and quality of source chemicals. Therefore, a **weight-of-evidence approach** combining computational, experimental and mechanistic information provides a more scientifically robust assessment.



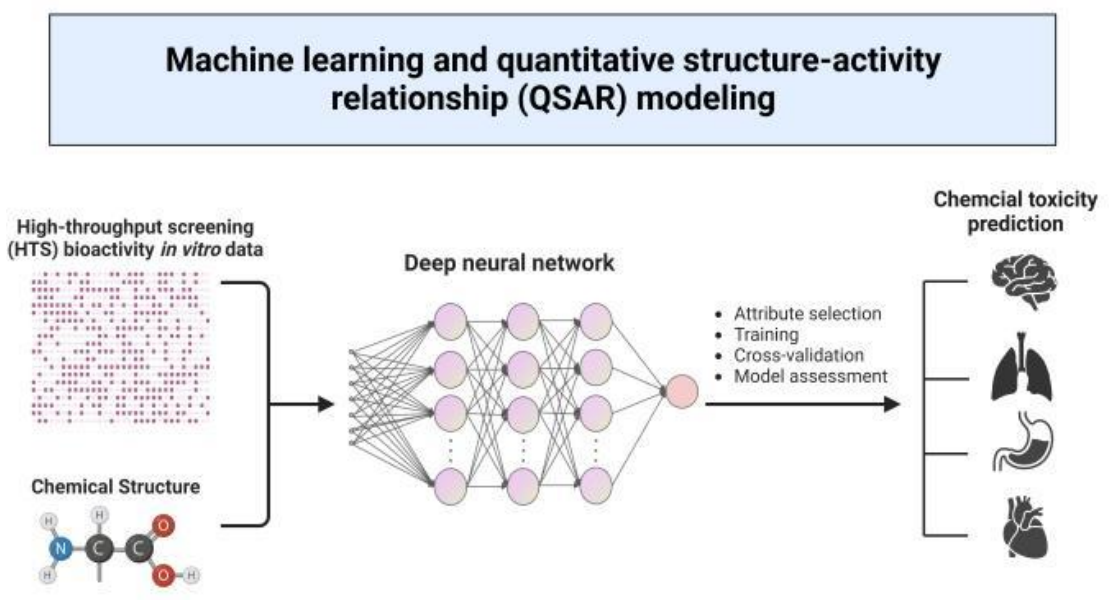
5. The Digital Toxicity Toolbox: Computational Methods and Predictive Approaches

The **digital toxicity toolbox** represents a collection of computational methods used to predict, evaluate, and interpret the toxicological properties of chemicals before extensive experimental testing. These approaches integrate chemical structure, biological information, molecular interactions, and existing toxicity data to generate predictions regarding potential hazards. The use of computational toxicology can reduce the dependence on animal

experiments, support early-stage screening, and help prioritize chemicals for further experimental investigation. Modern digital toxicity assessment commonly combines **quantitative structure–activity relationship (QSAR) models, read-across, molecular docking, molecular dynamics, machine learning, artificial intelligence, and toxicokinetic modelling**.[20,22]

5.1 Quantitative Structure–Activity Relationship (QSAR)

QSAR is one of the most established computational approaches in toxicity prediction. It is based on the assumption that the biological or toxicological activity of a chemical is related to its physicochemical and structural characteristics. Molecular descriptors such as **molecular weight, lipophilicity, hydrogen-bonding capacity, polar surface area, and electronic properties** can be used to construct mathematical relationships between chemical structure and toxicological endpoints. QSAR models may be applied to predict endpoints such as acute toxicity, mutagenicity, carcinogenicity, skin sensitization, and aquatic toxicity.[20, 23]



5.2 Read-Across and Chemical Similarity

Read-across predicts the toxicity of an untested chemical by using experimental information from structurally or mechanistically similar chemicals. Chemical similarity may be determined using molecular fingerprints, structural descriptors, or similarity coefficients. This approach is particularly useful when experimental data are unavailable for a newly developed chemical. However, the reliability of read-across depends on selecting appropriate analogues

and demonstrating that the chemicals have sufficiently similar toxicological mechanisms.[21, 24]

5.3 Molecular Docking and Molecular Dynamics

Molecular docking is a computational technique used to investigate the possible interaction between a chemical and a biological target such as an enzyme, receptor, or protein. It can provide information about **binding orientation, binding interactions, and potential molecular targets** associated with toxicity. Molecular dynamics simulations can further investigate the stability and behaviour of chemical–protein complexes over time. These approaches are useful for understanding the possible **mechanism of action (MoA)** underlying toxic effects.[25, 26]

5.4 Machine Learning and Artificial Intelligence

Machine learning (ML) and artificial intelligence (AI) have expanded the capabilities of computational toxicology by allowing models to identify complex relationships within large chemical and biological datasets. Algorithms such as **random forests, support vector machines, artificial neural networks, gradient boosting, and deep learning** can be trained using experimentally characterized compounds and subsequently applied to predict toxicity for new chemicals.[22, 27] The performance of these models depends strongly on the quality, diversity, and relevance of the training data. Therefore, model validation, applicability-domain assessment, and interpretability are important for reliable toxicity prediction.[27, 28]

5.5 Toxicokinetic and Toxicodynamic Modelling

Computational toxicokinetic approaches estimate how a chemical is **absorbed, distributed, metabolized, and excreted (ADME)** within the body. Physiologically based toxicokinetic (PBTK/PBPK) models can simulate chemical concentrations in different tissues and organs. When combined with toxicodynamic information, these models can help relate chemical exposure to biological responses. Such approaches are valuable for understanding dose–response relationships and supporting human health risk assessment.[29]

Table: Major Components of the Digital Toxicity Toolbox.

Computational approach	Major purpose	Typical application
QSAR	Relates chemical structure to toxicity	Mutagenicity, acute toxicity, sensitization
Read-across	Uses data from similar chemicals	Data-gap filling
Molecular docking	Predicts chemical–target interactions	Mechanistic toxicity assessment
Molecular dynamics	Studies stability of molecular interactions	Protein–ligand interaction analysis
Machine learning/AI	Identifies complex patterns in datasets	Toxicity classification and prediction
PBPK/PBTK modelling	Predicts chemical behaviour in the body	Exposure and risk assessment
Network/pathway analysis	Connects molecular targets and biological pathways	Mechanism-of-action analysis

Diagram: Digital Toxicity Toolbox Workflow

The integration of multiple computational approaches provides a more comprehensive understanding of chemical toxicity than relying on a single prediction method. For example, QSAR can provide an initial toxicity estimate, read-across can support data-gap filling, molecular docking can provide mechanistic information, and machine-learning models can integrate multiple chemical and biological features. The final computational prediction should ideally be supported by experimental evidence, especially when the prediction is intended for regulatory or high-confidence decision-making.[22, 27, 29]

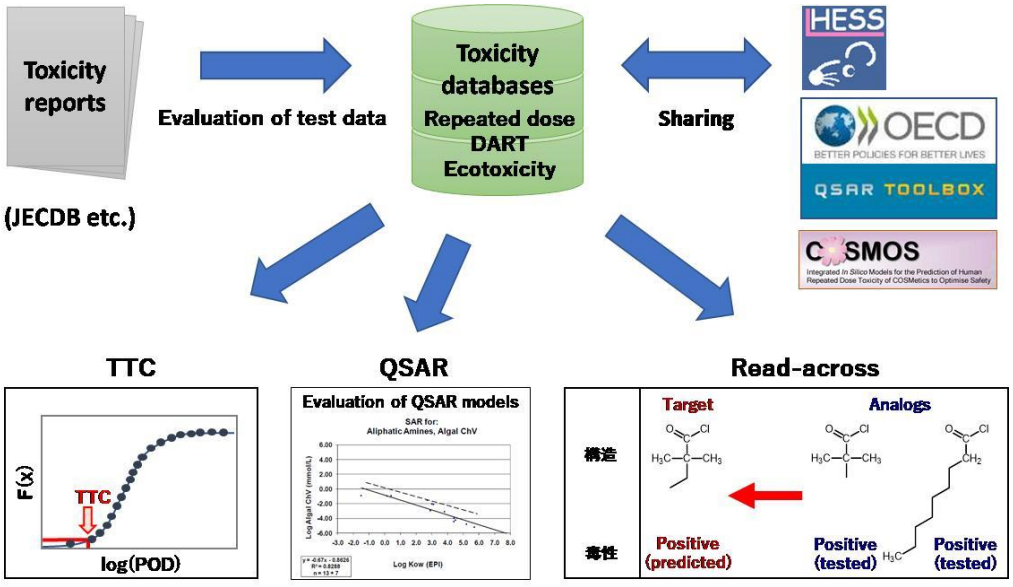
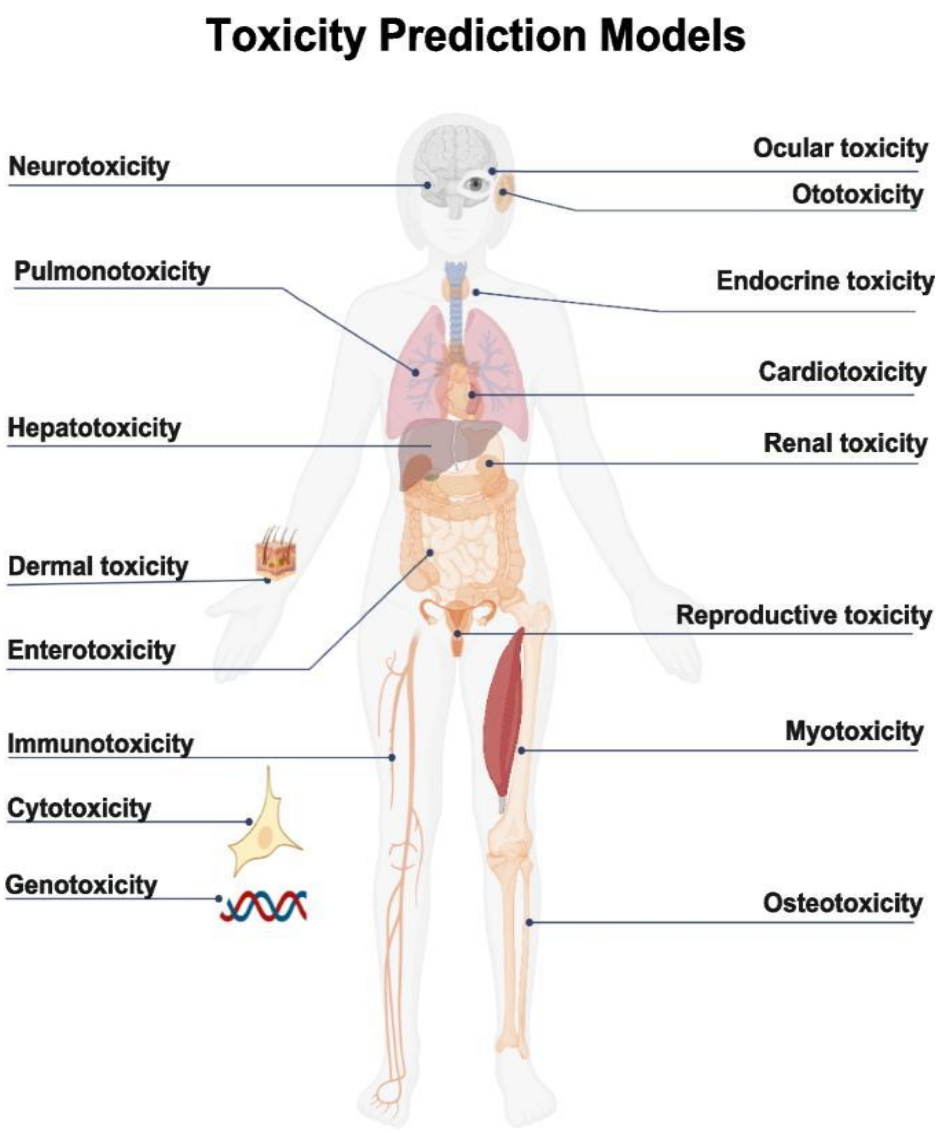


Figure. Digital toxicity toolbox showing integration of computational methods for toxicity prediction and risk assessment.

6. Major Toxicity End Points under the Computational Lens

Computational toxicology provides a systematic approach for predicting different toxicity endpoints by integrating chemical structure, molecular descriptors, biological targets, toxicity databases, and mechanistic information. Instead of evaluating toxicity only through conventional experimental testing, computational methods such as quantitative structure–activity relationship (QSAR), read-across, molecular docking, machine learning (ML), artificial intelligence (AI), toxicokinetic modelling, and adverse outcome pathway (AOP)-based approaches can be used for early hazard identification and prioritization. Major human-health toxicity endpoints that can be investigated computationally include **cardiotoxicity, hepatotoxicity, nephrotoxicity, neurotoxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, immunotoxicity, respiratory toxicity, and acute or systemic toxicity**.



6.1 Cardiotoxicity

Cardiotoxicity refers to adverse effects of chemicals or drugs on the heart and cardiovascular system. Computational prediction of cardiotoxicity has become an important component of drug and chemical safety assessment. In silico approaches can identify potential interactions with cardiac ion channels, receptors, enzymes, and other molecular targets. For example, computational models may be used to predict interactions with ion channels involved in cardiac electrical activity and to identify structural features associated with arrhythmogenic potential. QSAR and machine-learning models can classify compounds according to their potential cardiotoxic effects, while molecular docking can provide information about possible interactions between a compound and a cardiac target. Recent computational studies have specifically included cardiotoxicity as one of the major organ-specific toxicity endpoints.

6.2 Hepatotoxicity

Hepatotoxicity is toxicity affecting the liver and is an important endpoint because the liver plays a central role in chemical metabolism and detoxification. Computational models can predict drug-induced liver injury (DILI), hepatocellular damage, enzyme-associated toxicity, and other liver-related adverse effects. QSAR models use molecular descriptors and structural fingerprints to identify chemical characteristics associated with hepatotoxicity. ML algorithms can further integrate chemical, biological, and toxicological information to improve prediction. Toxicokinetic modelling is also useful because metabolism and bioactivation can strongly influence liver toxicity.

6.3 Nephrotoxicity

Nephrotoxicity involves adverse effects on the kidneys, including damage to renal cells and impairment of kidney function. Computational approaches can predict potential interactions of chemicals with renal transporters, enzymes, and molecular pathways. QSAR, molecular docking, read-across, and ML models can be used to identify chemicals with structural or biological characteristics associated with renal toxicity. Integration of toxicokinetic information is particularly useful because renal exposure and elimination influence the concentration of chemicals reaching kidney tissues. Computational prediction of drug-induced nephrotoxicity is increasingly incorporated into multi-endpoint toxicity modelling.

6.4 Neurotoxicity

Neurotoxicity refers to adverse effects on the nervous system and may involve neuronal damage, altered neurotransmission, developmental effects, or changes in nervous-system

function. Computational toxicology can investigate neurotoxic mechanisms by analysing chemical–target interactions, biological pathways, and molecular similarity. QSAR and ML models can be trained using existing neurotoxicity data, while AOP-based approaches can connect molecular initiating events with downstream neurological outcomes. Computational methods are particularly useful for screening large numbers of chemicals before more detailed experimental investigation.

6.5 Genotoxicity and Mutagenicity

Genotoxicity describes the ability of a chemical to damage genetic material, whereas mutagenicity refers to the induction of genetic mutations. Computational prediction of genotoxicity commonly uses QSAR models, structural alerts, molecular fingerprints, and ML algorithms. Ames mutagenicity is one of the commonly modelled endpoints in computational toxicology. Structural alerts can identify chemical substructures associated with DNA-reactive or mutagenic activity. Multiple computational predictions can also be combined to increase confidence, provided that the models are appropriately validated and their applicability domains are considered.

6.6 Carcinogenicity

Carcinogenicity is the potential of a chemical to contribute to cancer development. Computational assessment of carcinogenicity may combine chemical structure, genotoxicity information, molecular targets, biological pathways, and mechanistic knowledge. QSAR models can identify structural patterns associated with carcinogenic chemicals, while AOP and pathway-based approaches can provide mechanistic interpretation. OECD guidance emphasizes that mechanistic considerations can improve the interpretation and application of QSAR predictions for carcinogenicity assessment.

6.7 Reproductive and Developmental Toxicity

Reproductive toxicity includes adverse effects on reproductive organs, fertility, reproductive performance, or reproductive processes. **Developmental toxicity** refers to adverse effects occurring during development, including effects on the embryo, fetus, or developing organism. Computational models can use molecular descriptors, endocrine-related targets, biological pathways, and chemical similarity to identify potential reproductive or developmental hazards. Endocrine-related computational approaches may also investigate interactions with estrogen, androgen, and thyroid signalling pathways.

6.8 Immunotoxicity

Immunotoxicity refers to harmful effects of chemicals on the immune system, including immune suppression, inappropriate immune activation, or altered immune signalling. Computational approaches can investigate chemical interactions with immune-related proteins and pathways and can integrate high-throughput screening data with molecular descriptors. AOP-based and pathway-based approaches are useful for linking molecular-level effects with broader immune-system outcomes. EPA computational toxicology research includes immunotoxicity among important toxicity areas for investigation.

6.9 Respiratory and Pulmonary Toxicity

Respiratory toxicity includes adverse effects on the lungs and respiratory tract. Computational assessment can involve prediction of respiratory irritation, pulmonary toxicity, sensitization, and chemical interactions with respiratory targets. QSAR, read-across, molecular docking, and mechanistic pathway approaches can be used to prioritize chemicals requiring further investigation. In silico assessment of organ toxicity increasingly considers **heart, kidney, and lung toxicities** as important organ-specific endpoints.

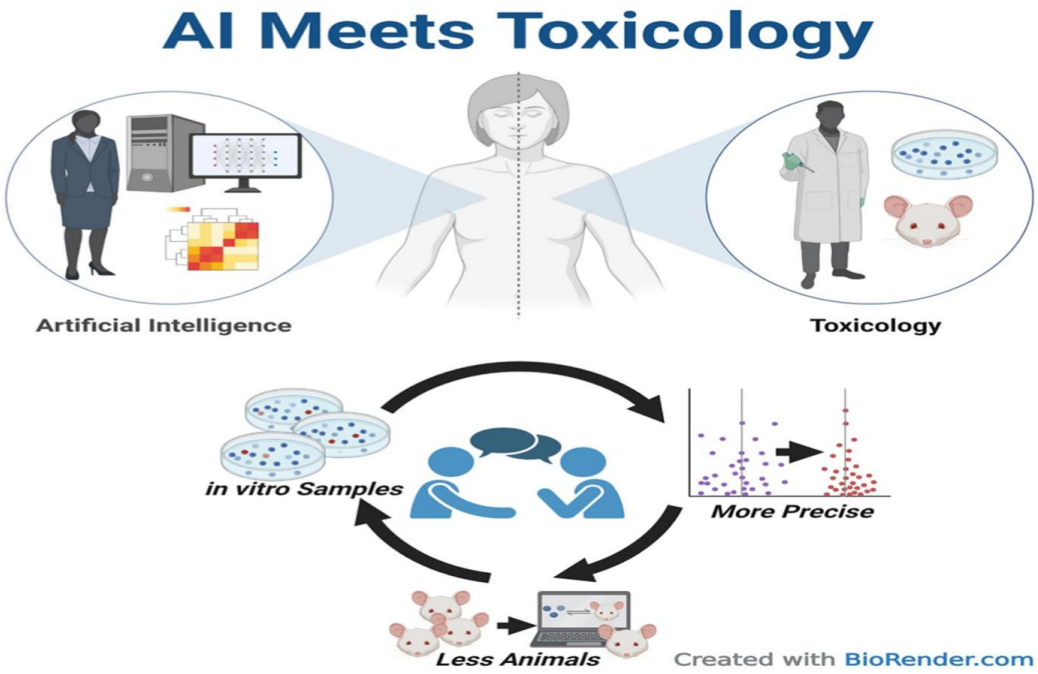
6.10 Integration of Multiple Toxicity Endpoints

A major advantage of modern computational toxicology is the ability to evaluate several toxicity endpoints simultaneously. Multi-endpoint ML and QSAR models can combine molecular descriptors, fingerprints, bioactivity data, and toxicity information to estimate the probability of different adverse outcomes. Recent computational frameworks have demonstrated simultaneous prediction of endpoints including **skin sensitization, respiratory toxicity, mutagenicity, hepatotoxicity, developmental toxicity, cardiotoxicity, nephrotoxicity, and neurotoxicity**.

Overall, the computational lens transforms toxicity assessment from a single-endpoint experimental process into a multi-endpoint, mechanism-oriented and data-driven workflow. The integration of QSAR, read-across, molecular docking, toxicokinetic modelling, AI/ML, and AOP approaches can support early identification of hazardous chemicals and help prioritize substances for further testing. However, computational predictions are most useful when they are transparently validated and combined with appropriate experimental evidence rather than being interpreted as independent confirmation of toxicity.

7. AI Meets Toxicology: Machine Learning, Deep Learning and Intelligent Prediction

Artificial intelligence (AI) has emerged as an important component of modern computational toxicology because of its ability to analyse large, complex, and heterogeneous datasets. Traditional toxicity prediction approaches generally depend on predefined molecular descriptors, structural alerts, or statistical relationships. In contrast, machine learning (ML) and deep learning (DL) can identify complex and nonlinear relationships between chemical structures, biological activities, molecular targets, and toxicological outcomes. This development has supported the transition from conventional QSAR towards data-driven and **intelligent toxicity prediction**.[39, 41] Recent reviews describe the increasing application of ML and DL to chemical toxicity prediction, including organ-specific toxicity, acute toxicity, carcinogenicity, and multi-endpoint modelling.



7.1 Machine Learning in Toxicology

Machine learning is a branch of AI in which algorithms learn patterns from existing data and use those patterns to make predictions for new observations. In computational toxicology, ML models are commonly trained using chemical structures, molecular descriptors, fingerprints, physicochemical properties, bioactivity data, and experimentally measured toxicity endpoints. Common algorithms include **random forest (RF), support vector machine (SVM), k-nearest neighbours (k-NN), decision trees, gradient boosting, and ensemble learning**.[39, 40]

For toxicity prediction, a chemical is first represented mathematically using molecular descriptors or fingerprints. The selected features are then provided to a machine-learning algorithm along with known toxicity outcomes. During training, the algorithm learns the relationship between the input features and the toxicity endpoint. Once validated, the trained model can be used to predict the toxicity of previously untested compounds. ML-based QSAR has therefore become an important approach for screening large numbers of chemicals rapidly.

Machine learning has been applied to several endpoints, including **acute toxicity, mutagenicity, hepatotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity, developmental toxicity, and carcinogenicity**. Multi-endpoint models can also predict several toxicity outcomes from the same chemical representation. Such approaches can be useful for prioritizing chemicals for further experimental testing and identifying substances that require more detailed safety evaluation.[39, 41]

7.2 Deep Learning and Toxicity Prediction

Deep learning is a subfield of machine learning that uses multi-layered artificial neural networks to learn increasingly complex representations from data. Unlike conventional ML methods, deep-learning models can learn useful features directly from suitable input representations, reducing the dependence on manually selected descriptors in some applications. **Deep neural networks (DNNs), convolutional neural networks (CNNs), recurrent neural networks (RNNs), graph neural networks (GNNs), and transformer-based architectures** have been investigated for chemical and toxicity prediction.[40, 42]

One of the important demonstrations of deep learning in toxicology was the **DeepTox** system developed for the Tox21 Data Challenge. The Tox21 challenge included thousands of compounds evaluated across multiple toxicity-related assays. DeepTox used chemical descriptors, neural-network models, model evaluation, and ensemble prediction to estimate toxicity. The study showed that deep learning could perform strongly on multiple toxicity assays and demonstrated the potential of multi-task learning for toxicity prediction.[43]

7.3 Graph Neural Networks and Molecular Representation

Chemical molecules can naturally be represented as graphs in which **atoms are nodes and chemical bonds are edges**. Graph neural networks can process this representation and learn relationships between molecular structure and biological activity. This is particularly useful

because the model can incorporate structural information without depending entirely on conventional fixed molecular descriptors.

Graph-based deep learning has contributed to the development of modern **deep QSAR** approaches. These models can learn molecular representations and potentially capture structural patterns associated with biological activity and toxicity. However, performance depends on the quality of the available data, chemical diversity, endpoint definition, and appropriate validation.[41, 42] The emergence of deep QSAR reflects the convergence of traditional QSAR modelling with modern AI and deep-learning technologies.

7.4 Intelligent Prediction of Toxicity Endpoints

AI-based systems can be applied to multiple toxicity endpoints rather than focusing on a single adverse effect. For example, a model can use chemical structure and biological information to estimate the probability of **hepatotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity, genotoxicity, reproductive toxicity, or developmental toxicity**. Multi-task learning is particularly useful because a single model can learn several related toxicity endpoints simultaneously. This may allow information shared between different biological responses to contribute to prediction performance.[41, 43]

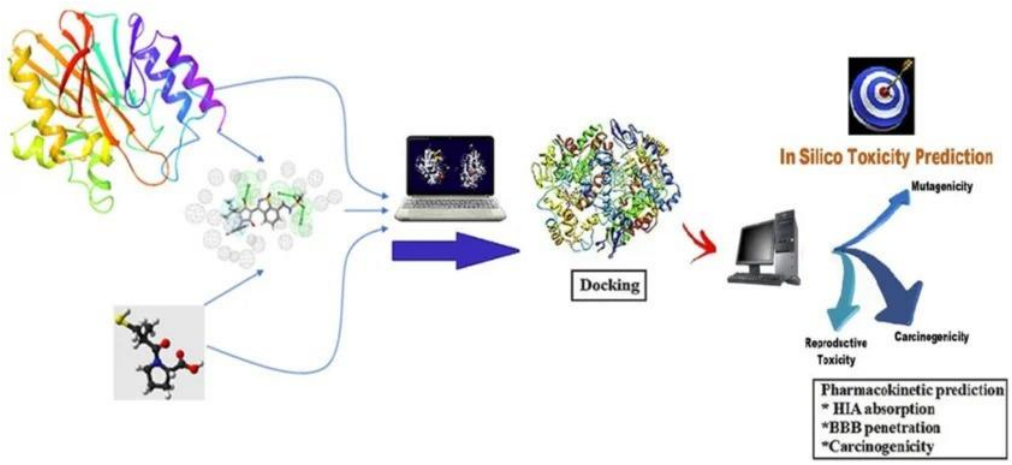
Deep-learning approaches have also been investigated for specific endpoints such as drug-induced liver injury. Reviews of computational liver-toxicity prediction indicate that deep learning can be incorporated into QSAR models and compared with traditional ML approaches, while issues such as interpretability and generalization remain important considerations.

7.5 Explainable AI in Toxicology

Although AI models can provide powerful predictions, some deep-learning models operate as **black-box systems**, making it difficult to understand why a particular chemical has been predicted as toxic. This is a major concern when computational predictions are used for scientific or regulatory decision-making. **Explainable artificial intelligence (XAI)** aims to identify the features or molecular regions that contribute to a prediction.

Methods such as feature importance analysis, molecular substructure interpretation, attention mechanisms, and other explanation techniques can help researchers understand model predictions. Explainability is particularly important in toxicology because researchers may

need to determine whether the predicted toxicity is associated with a chemically or biologically plausible mechanism. Good-practice guidance for ML-based toxicological QSAR emphasizes data quality, appropriate feature selection, validation, generalisability, and consideration of uncertainty.[40]



7.6 Advantages of AI-Based Toxicity Prediction

AI and ML provide several potential advantages in computational toxicology. They can process large datasets rapidly, identify nonlinear relationships, support high-throughput screening, and reduce the amount of experimental testing required for initial chemical prioritization. AI can also integrate different types of information, including **chemical structure, molecular descriptors, bioassay data, omics information, and biological pathway data**. This creates opportunities for more comprehensive and mechanism-oriented toxicity assessment.[39, 41]

Another important advantage is the possibility of **early toxicity prediction during drug discovery**. Candidate molecules can be computationally screened before extensive experimental development, allowing potentially problematic structures to be identified at an earlier stage. In this way, AI-based prediction can contribute to the selection and optimization of safer chemical candidates.

7.7 Limitations and Challenges

Despite rapid progress, AI-based toxicity prediction has several limitations. The performance of an AI model is strongly dependent on the **quality, consistency, size, and diversity of the training dataset**. Incomplete or biased toxicity data may lead to unreliable predictions. Chemical datasets may also contain structurally similar compounds in both training and test

sets, which can produce overly optimistic estimates if validation is not carefully designed. Therefore, appropriate data splitting, cross-validation, external validation, and applicability-domain assessment are essential.[40,41] Another challenge is **interpretability and uncertainty**. A highly accurate prediction is not automatically a reliable prediction for every new chemical. Models may perform poorly when applied to compounds outside their training domain. Recent work on conformal prediction demonstrates one approach for associating toxicity predictions with confidence information, helping users understand the reliability of individual predictions.[44]

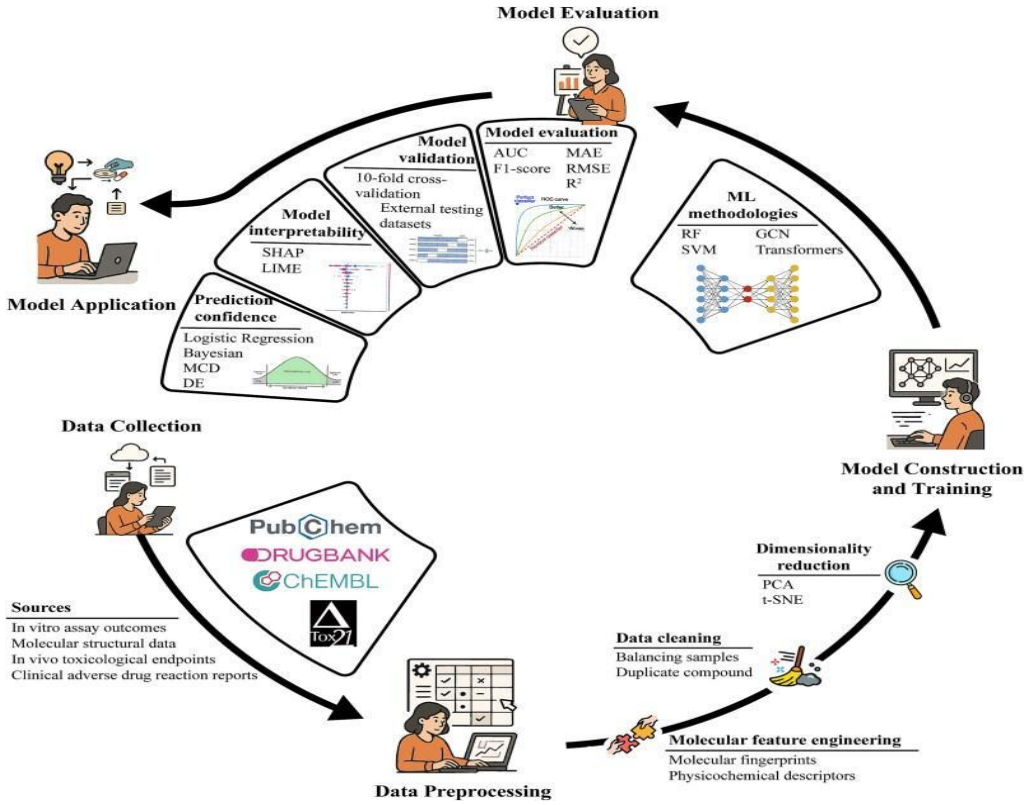


Figure 7: AI-based workflow for intelligent toxicity prediction using machine learning, deep learning and graph-based approaches.

Table: AI Approaches Used in Computational Toxicology.

AI approach	Main principle	Application in toxicology
Random Forest	Combines multiple decision trees	Toxicity classification and QSAR
Support Vector Machine	Finds optimal decision boundaries	Binary toxicity prediction
Gradient Boosting	Sequentially improves weak learners	Toxicity and ADMET prediction
Deep Neural Network	Learns nonlinear molecular relationships	Multi-endpoint toxicity prediction
CNN	Learns spatial/local patterns	Molecular or image-based toxicity prediction

Graph Neural Network	Learns directly from molecular graphs	Structure–toxicity prediction
Multi-task Learning	Predicts multiple endpoints simultaneously	Tox21-type multi-endpoint screening
Explainable AI	Identifies factors supporting predictions	Interpretation and mechanistic analysis
Conformal Prediction	Provides prediction with confidence information	Uncertainty-aware toxicity prediction

7.8 Future Perspective

The future of AI in toxicology is moving towards multi-modal, explainable, mechanism-aware, and uncertainty-aware prediction. Integration of chemical structures with transcriptomics, proteomics, high-content screening, toxicogenomics, and other biological datasets may improve mechanistic understanding of toxicity. Hybrid models that combine mechanistic toxicology with machine learning may also help overcome some limitations of purely data-driven approaches. Recent developments in deep QSAR, graph-based modelling, generative AI, and explainable prediction indicate that computational toxicology is progressing from simple toxicity classification towards integrated intelligent safety assessment.[41, 45]

However, AI should be considered a decision-support technology rather than an automatic replacement for all experimental evidence. Reliable application requires high-quality data, transparent model development, appropriate validation, applicability-domain assessment, and clear communication of uncertainty. With these safeguards, AI and ML can support faster chemical screening, prioritization of substances, identification of potential toxic mechanisms, and more efficient safety assessment.[40, 41]

8. Applications in Modern Drug Discovery: From Molecule to Safer Candidate

Modern drug discovery is a complex and time-consuming process in which a large number of chemical molecules are evaluated before a small number of candidates progress to preclinical and clinical development. A major challenge is that a molecule may show good potency against its intended biological target but later fail because of poor absorption, distribution, metabolism, excretion, or toxicity (ADMET) properties. Therefore, computational toxicology and in silico ADMET prediction are increasingly incorporated into drug discovery from the **early molecular design stage** rather than being used only after a lead compound has been selected. Early computational assessment can help identify potentially problematic molecules, prioritize promising candidates, and guide structural optimization.[1, 48]

8.1 From Molecular Design to Safety Screening

The modern drug discovery process begins with the identification of a biological target and the design or selection of molecules capable of interacting with that target. Molecular docking, pharmacophore modelling, molecular dynamics, and virtual screening can be used to identify compounds with desirable target-binding characteristics. However, high target affinity alone does not guarantee that a compound will become a successful drug. The molecule must also possess suitable physicochemical, pharmacokinetic, and safety properties.

Computational approaches therefore allow **efficacy and safety to be evaluated in parallel**. Molecular properties such as molecular weight, lipophilicity, hydrogen-bonding capacity, polarity, solubility, and structural alerts can be evaluated before synthesis or extensive experimental testing. This approach helps researchers identify compounds that may have favourable biological activity but unacceptable ADMET characteristics at an early stage.[1, 47]

8.2 Virtual Screening and Lead Identification

Virtual screening is an important application of computational methods in modern drug discovery. Large chemical libraries can be screened computationally to identify molecules that are likely to interact with a particular biological target. Docking-based virtual screening evaluates possible binding modes, whereas ligand-based methods identify compounds that are structurally or pharmacologically similar to known active molecules.

The advantage of virtual screening is that thousands or millions of compounds can be prioritized computationally before a smaller number are selected for laboratory testing. Toxicity-related filters can be incorporated into this process so that compounds with undesirable structural features or predicted safety liabilities can be deprioritized. Thus, virtual screening can move beyond identifying molecules that are simply **active** toward identifying molecules that are potentially **active and developable**.[48, 49]

8.3 In Silico ADMET Profiling

ADMET profiling is one of the most important applications of computational toxicology in drug discovery. The five major components are **absorption, distribution, metabolism, excretion, and toxicity**. Computational models can estimate properties such as aqueous solubility, intestinal absorption, permeability, plasma protein binding, blood–brain barrier penetration, cytochrome P450 interactions, metabolic stability, renal clearance, and several toxicity endpoints.[1, 50]

Early ADMET prediction can help identify compounds with poor pharmacokinetic characteristics before they enter expensive experimental studies. For example, a compound with excellent target potency but very poor predicted solubility or excessive metabolic instability may require structural modification. Similarly, prediction of potential hepatotoxicity, cardiotoxicity, mutagenicity, or other toxicity endpoints can alert researchers to possible safety concerns. Current computational platforms provide predictions across multiple ADMET endpoints and include QSAR-, machine-learning-, and graph-based approaches.

8.4 Structure Optimization for Safer Candidates

Once a lead molecule has been identified, medicinal chemists modify its chemical structure to improve potency, selectivity, pharmacokinetics, and safety. Computational toxicology can support this **lead optimization** process by predicting how structural modifications may influence ADMET properties.

For example, if a particular structural group is associated with metabolic instability or toxicity, computational models can identify alternative substitutions that may reduce the predicted liability. Similarly, molecular descriptors and ML models can help compare different analogues and identify compounds with a more balanced property profile. This creates an iterative cycle in which **design → prediction → synthesis → testing → redesign** is repeated until a suitable candidate is obtained.[47, 50]

8.5 Prediction of Organ-Specific Toxicity

Modern computational systems can predict organ-specific toxicity during drug discovery. Important endpoints include **hepatotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity, pulmonary toxicity, and reproductive or developmental toxicity**. ML and deep-learning models can analyse chemical structures together with biological data to identify patterns associated with these adverse outcomes.

Cardiotoxicity prediction is particularly relevant because interactions with cardiac ion channels and other cardiovascular targets can influence the safety profile of drug candidates. Similarly, computational hepatotoxicity models can identify compounds associated with drug-induced liver injury, while renal toxicity models can help identify possible kidney-related liabilities. Such predictions allow researchers to investigate potentially problematic candidates before extensive animal or clinical studies.[48, 51]

8.6 Artificial Intelligence in Candidate Prioritization

Artificial intelligence and machine learning have expanded the ability to integrate multiple sources of information during drug discovery. Instead of considering each property separately, AI models can analyse chemical structure, biological activity, ADMET characteristics, and toxicity data simultaneously. Deep-learning and graph neural network models can learn molecular representations and identify complex relationships between chemical structure and biological or toxicological responses.[51, 52]

Multi-task learning is particularly useful because several related ADMET or toxicity endpoints can be predicted using a common computational framework. Recent developments also include multimodal models that integrate chemical, biological, genomic, and phenotypic information. These approaches support more comprehensive evaluation of drug candidates rather than relying on a single toxicity endpoint.

8.7 Toxicity-Based Candidate Deprioritization

An important application of computational toxicology is the **early elimination or deprioritization of compounds with unacceptable safety predictions**. If a molecule shows strong target activity but is consistently predicted to have serious toxicity liabilities, researchers can investigate alternative chemical structures before investing substantial resources in its development.

This approach does not mean that a computational prediction automatically proves that a compound is toxic. Instead, it provides an early warning that can be investigated using appropriate experimental methods. Combining computational predictions with in vitro and other experimental data provides a more informed basis for selecting candidates for further development.[48, 51]

8.8 Integration with Experimental Validation

Computational prediction works most effectively when integrated with experimental testing. After virtual screening and computational ADMET evaluation, selected compounds can undergo biochemical, cellular, and pharmacological assays. Experimental results can then be used to refine computational models and improve predictions for subsequent compound series.

This creates a **closed-loop drug discovery system**, where computational predictions guide experiments and experimental observations improve computational models. Such model-informed approaches are increasingly relevant to modern drug development.

8.9 From Molecule to Safer Candidate

The overall objective is not simply to identify the most potent molecule but to develop a compound with a balanced combination of **target activity, selectivity, pharmacokinetics, safety, and developability**. Computational toxicology contributes to this process by allowing safety-related properties to be considered earlier and repeatedly throughout molecular optimization.

Thus, the modern workflow can be described as

TARGET IDENTIFICATION
▼
MOLECULAR DESIGN
▼
VIRTUAL SCREENING
▼
POTENCY & SELECTIVITY

PREDICTION
▼
IN SILICO ADMET SCREENING
▼
ADME Prediction **Toxicity Prediction** **Off-target Prediction**
▼
CANDIDATE PRIORITIZATION
▼
STRUCTURAL OPTIMIZATION
▼
IN VITRO EXPERIMENTATION
▼
IN VIVO / PRECLINICAL EVALUATION
▼
SAFER CANDIDATE
▼
FURTHER DEVELOPMENT

8.10 Role of Computational Tools in Reducing Attrition

Poor pharmacokinetic properties and toxicity have historically contributed substantially to failure during drug development. Consequently, ADMET prediction is increasingly

performed during early discovery rather than being postponed until later stages. Early computational evaluation allows researchers to identify potential liabilities while chemical structures can still be modified relatively easily.[1, 47]

Modern computational platforms such as SwissADME, pkCSM, ADMETlab, admetSAR, ADMET-AI, and ProTox provide different combinations of physicochemical, pharmacokinetic, and toxicity predictions. These platforms illustrate the movement from individual prediction models toward integrated ADMET assessment systems.

8.11 Future Perspective

The future of computational drug discovery is likely to involve increasingly integrated systems in which generative AI, molecular design, ADMET prediction, toxicity modelling, and experimental data are connected in a continuous optimization cycle. Generative models can propose new molecular structures, while predictive models can evaluate their potency, pharmacokinetics, and toxicity before synthesis. This creates the possibility of designing molecules according to multiple objectives simultaneously rather than optimizing potency alone.[51, 52]

However, computational predictions should be interpreted according to their applicability domain, validation performance, uncertainty, and data quality. AI models can support candidate prioritization, but experimental confirmation remains important, particularly for high-consequence safety decisions. The current direction of computational toxicology is therefore toward integrated, interpretable, uncertainty-aware, and experimentally validated drug discovery.

Overall, computational toxicology has changed the concept of drug discovery from a sequential process of “design first and test toxicity later” toward a more integrated approach in which efficacy, ADME, toxicity, and safety are considered from the beginning of molecular design. This integration can support the identification and optimization of drug candidates with a more balanced therapeutic and safety profile.[1, 54]

9. Advantages of In Silico Toxicity Screening: Faster, Smarter and More Ethical

1. Faster toxicity prediction

In silico methods can predict the potential toxicity of large numbers of chemical compounds within a short period. Unlike conventional toxicity testing, which may require weeks or

months, computational screening provides rapid preliminary information and helps researchers identify potentially toxic compounds at an early stage of drug discovery.[55]

2. Early identification of toxic compounds

Computational toxicity screening can identify undesirable toxicological properties before compounds enter extensive experimental testing. Early detection helps researchers eliminate unsuitable candidates and focus on molecules with better safety profiles.[3]

3. Cost-effective approach

In silico screening can reduce the cost associated with large-scale laboratory experiments and animal studies. By prioritizing compounds for experimental validation, computational approaches help use laboratory resources more efficiently.[56]

4. High-throughput screening

Thousands of compounds can be screened computationally in a relatively short time. This makes in silico approaches particularly useful during early drug discovery, where large chemical libraries need to be evaluated and prioritized.[55]

5. Reduction in animal experimentation

Computational toxicity prediction can reduce the number of animals required for conventional toxicity studies. It supports the principles of Replacement, Reduction and Refinement (3Rs) by helping researchers identify compounds that may not require immediate animal testing.[57]

6. Prediction of multiple toxicity endpoints

In silico models can be developed to predict different toxicological endpoints, including hepatotoxicity, cardiotoxicity, nephrotoxicity, mutagenicity, carcinogenicity and reproductive toxicity. This provides a broader safety assessment during drug development.[50]

7. Supports safer lead optimization

Toxicity predictions can be incorporated into the lead-optimization process. When a structural feature is associated with toxicity, medicinal chemists can modify the chemical structure to reduce the predicted toxic effect while attempting to maintain the desired pharmacological activity.[3]

8. Uses existing toxicological knowledge

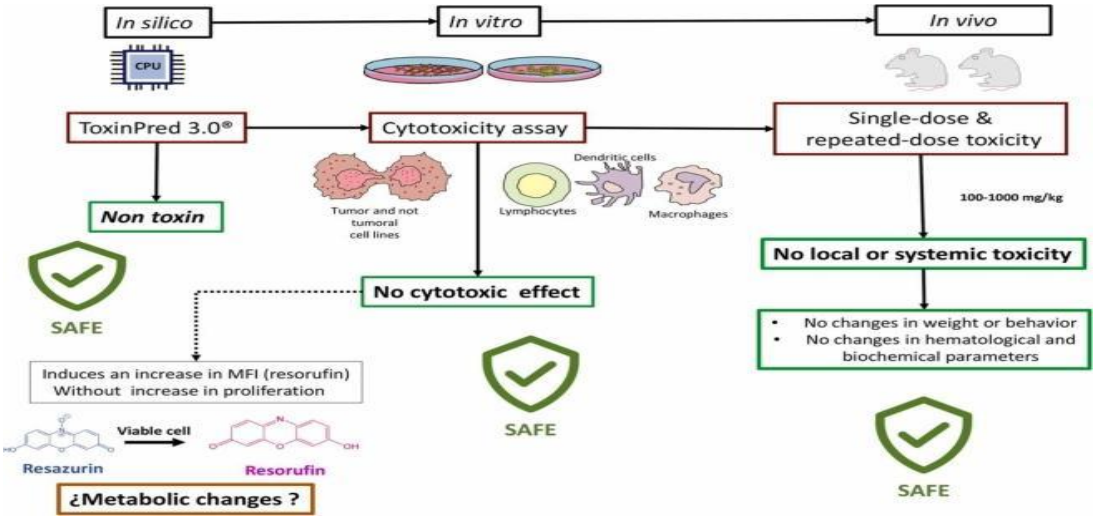
QSAR models, machine-learning algorithms and read-across approaches can utilize previously generated experimental data. Therefore, information obtained from known chemicals can support toxicity prediction for structurally or biologically related compounds.[58]

9. Reproducibility and standardization

Once a computational model has been properly developed and validated, it can be applied systematically to new compounds using defined parameters. This can improve consistency and reproducibility in preliminary toxicity assessment.[59]

10. Ethical and sustainable drug discovery

By reducing unnecessary laboratory and animal experiments, computational toxicology contributes to a more ethical and sustainable approach to drug development. It complements experimental methods and supports the growing use of New Approach Methodologies (NAMs) in modern safety assessment.[57, 59]



10. The Hidden Challenges: Limitations, Data Gaps and Experimental Validation

10.1 Limited Quality and Availability of Toxicity Data

In silico toxicity models depend strongly on the quality and completeness of the datasets used for model development. Toxicological databases may contain missing values, inconsistent experimental conditions, different assay protocols and variations in endpoint definitions. Such differences can affect model performance and reduce the reliability of predictions for new chemical entities.[60]

10.2 Data Imbalance and Dataset Bias

Many toxicity datasets contain an unequal distribution of toxic and non-toxic compounds. This imbalance can cause machine-learning models to favour the majority class and may produce misleading accuracy values. In addition, datasets generated from a limited chemical space may introduce bias and reduce the generalizability of the model. Appropriate dataset curation, balancing and independent validation are therefore important.[61]

10.3 Applicability Domain and Structural Diversity

An in silico model is generally more reliable for compounds that fall within the chemical and biological space represented by its training data. Predictions for structurally different molecules may involve extrapolation and therefore carry greater uncertainty. Defining the applicability domain is consequently an important requirement for reliable QSAR and machine-learning-based toxicity prediction.[57]

10.4 Biological Complexity and Mechanistic Limitations

Toxicity is a complex biological phenomenon involving absorption, distribution, metabolism, excretion, molecular interactions, signalling pathways and interactions between different organs. A computational model based primarily on molecular structure may not completely reproduce these biological processes. Metabolism-dependent toxicity and complex organ-level effects can therefore remain difficult to predict accurately.[62]

10.5 Black-Box Nature and Model Interpretability

Advanced machine-learning and deep-learning models can identify complex relationships within large datasets, but their predictions may sometimes be difficult to interpret mechanistically. Lack of transparency regarding why a particular compound is predicted to be toxic can reduce confidence in the model and may create challenges in scientific and regulatory applications. Explainable and interpretable AI approaches are therefore increasingly important in computational toxicology.[63]

10.6 Overfitting, False Predictions and Reproducibility

A model may show excellent performance with its training dataset but perform poorly when applied to completely new chemicals. This problem, known as overfitting, occurs when the model learns specific characteristics or noise from the training data rather than general toxicological relationships. External validation, independent test sets and standardized

reporting are essential to identify false-positive and false-negative predictions and improve reproducibility.[64]

10.7 Importance of In Vitro Experimental Validation

In vitro validation provides an important bridge between computational prediction and biological observation. Cell-based assays, biochemical assays, organ-specific models and advanced 3D cellular systems can be used to determine whether a predicted toxic effect occurs under controlled biological conditions. In vitro experiments can also provide information about concentration–response relationships, cellular viability, oxidative stress, mitochondrial dysfunction and other mechanisms of toxicity. Thus, in vitro testing can confirm and refine computational predictions before further testing is considered.[65]

10.8 Importance of In Vivo Experimental Validation

In vivo studies provide information about the response of an integrated biological system that may not be completely captured by computational or isolated in vitro models. They can provide information regarding systemic toxicity, organ-level effects, pharmacokinetics and the relationship between exposure and biological response. However, because animal studies involve ethical, scientific and resource considerations, they should be performed when scientifically justified and when appropriate alternative methods cannot adequately address the research question.[66]

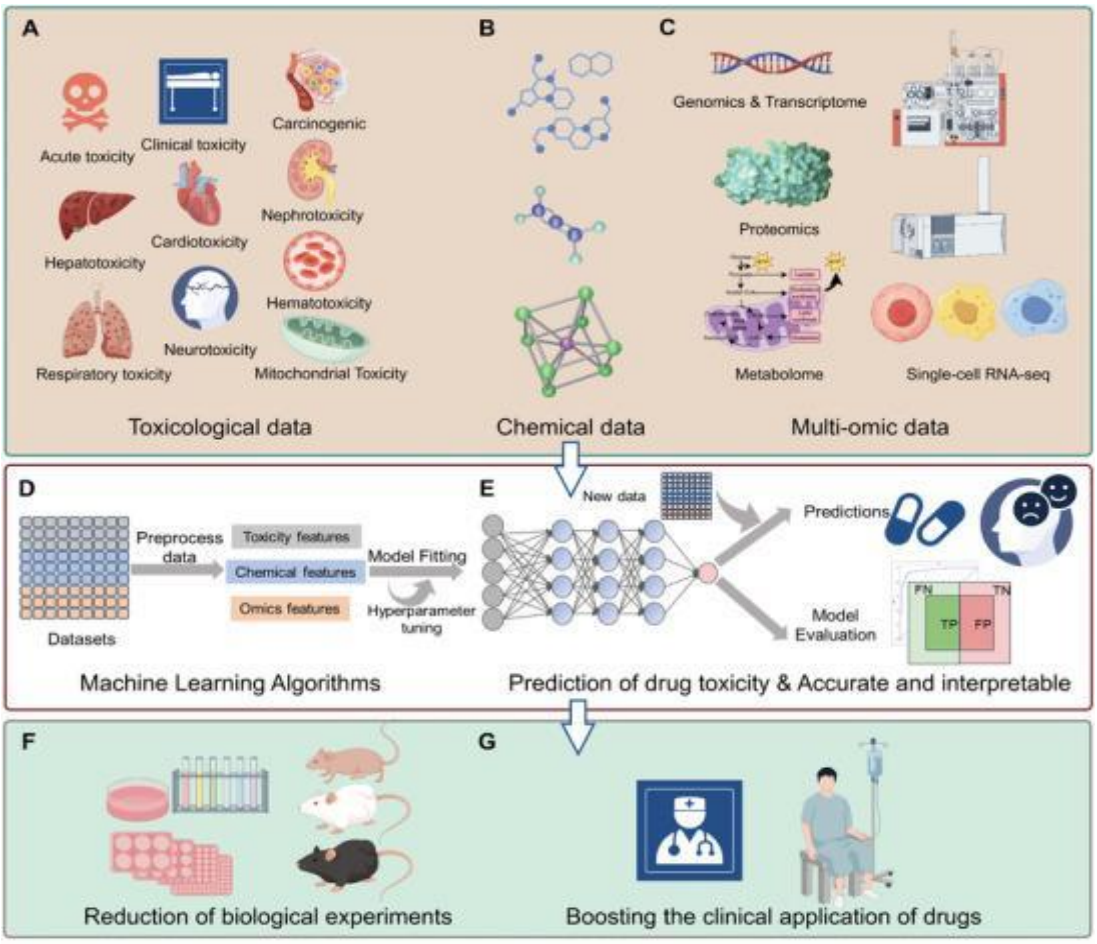
10.9 Integration of In Silico, In Vitro and In Vivo Approaches

The greatest value can be obtained when computational and experimental approaches are used together. **In silico methods** can be used for rapid screening and prioritization, **in vitro methods** can provide cellular and mechanistic evidence, and **in vivo studies**, when necessary, can provide information about integrated systemic responses. Combining these approaches through a weight-of-evidence strategy can improve confidence in toxicity assessment while helping to reduce unnecessary experimental testing.[67]

10.10 Need for Human-Relevant Validation and Regulatory Acceptance

A major challenge in toxicity prediction is translating computational or experimental findings into reliable information about human safety. Human-relevant models such as advanced cell cultures, 3D tissue models and organ-on-chip systems are being explored to improve biological relevance. At the same time, computational models require appropriate validation, defined applicability domains and transparent reporting before they can be confidently used

in regulatory decision-making. Therefore, future toxicity assessment is likely to depend on the **integrated use of validated in silico models, human-relevant in vitro systems and carefully justified in vivo studies.**[68]



11. Future Horizon: AI-Driven and Personalised Toxicology

The future of toxicology is moving towards **AI-driven, data-integrated and personalised safety assessment**. Advances in machine learning, deep learning, toxicogenomics, multi-omics, high-throughput screening and human-relevant experimental models are creating opportunities to predict toxicity more rapidly and at greater biological resolution. Recent reviews describe AI and multimodal data fusion as important developments in modern drug-toxicity prediction.

11.1 AI-Driven Toxicity Prediction

Artificial intelligence can analyse large and complex chemical and biological datasets to identify relationships between molecular structure and toxicological outcomes. Machine-learning, deep-learning and graph-based models can be applied to endpoints such as

hepatotoxicity, cardiotoxicity, nephrotoxicity, mutagenicity and carcinogenicity. The FDA's **SafetAI** initiative is an example of ongoing development of deep-learning models for these safety endpoints before clinical trials.

11.2 Personalised Toxicology

Future toxicity assessment may increasingly consider **individual biological variability** rather than assuming that all individuals respond identically to a chemical or drug. Genetic variation, genomic profiles, previous drug exposure and other biological characteristics can potentially be integrated with toxicological data to identify individuals or populations with different susceptibility to adverse effects. AI can assist in analysing these high-dimensional datasets and developing patient-specific toxicity predictions.

11.3 Toxicogenomics and Multi-Omics Integration

Integration of **genomics, transcriptomics, proteomics and metabolomics** with chemical and toxicity data can provide mechanistic information about how compounds produce adverse effects. AI is particularly useful for identifying patterns across these large datasets. Such approaches may help connect molecular changes with pathways, biomarkers and adverse outcomes, supporting more mechanism-based toxicity prediction.

11.4 AI-Based Digital Twins and Virtual Models

A specific emerging application is the development of **virtual biological models or digital twins**. The FDA's AnimalGAN initiative is investigating generative AI to produce virtual animal-study data from existing toxicological information, with the objective of reducing reliance on animal experiments. This represents a developing application rather than a replacement that is already universally validated for all toxicity testing.

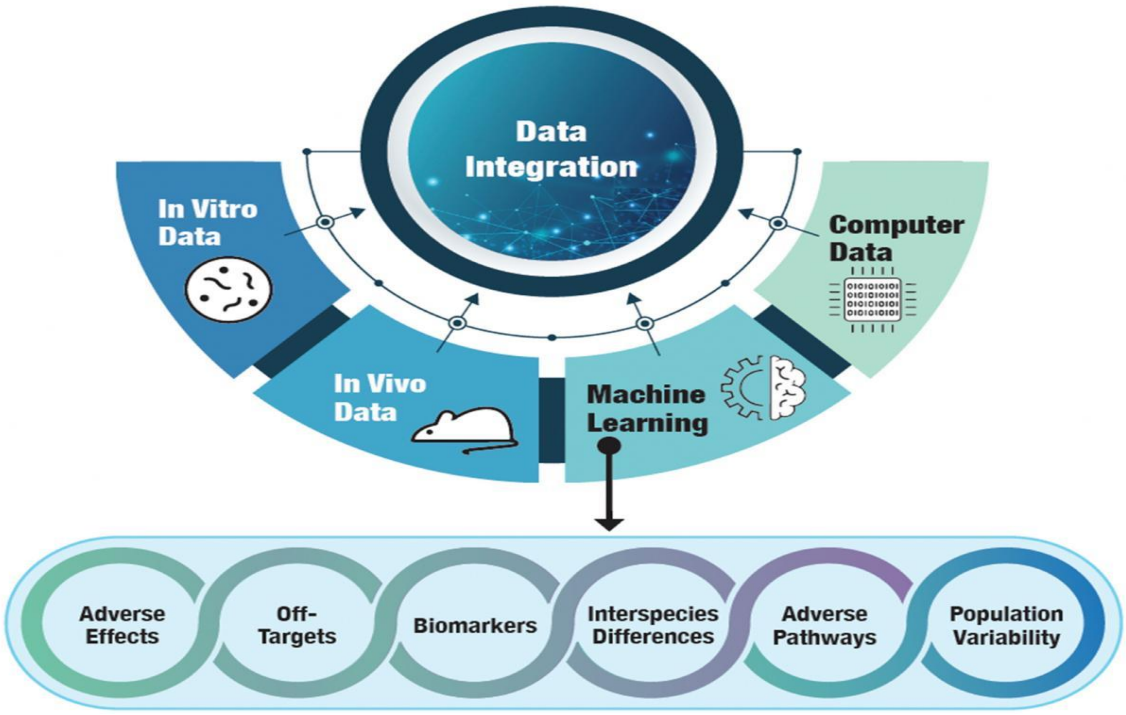
11.5 AI for In Vitro-to-In Vivo Translation

AI may help overcome one of the important challenges in toxicology: translating results obtained from cell-based experiments into expected responses in an intact organism. The FDA's **TranslAI** initiative specifically investigates AI approaches for in vitro-to-in vivo extrapolation (IVIVE) and translation across biological systems.

11.6 Personalised Prediction of Drug-Induced Organ Toxicity

A particularly relevant future application is **individualised prediction of organ-specific toxicity**, such as drug-induced liver injury (DILI). AI models can integrate chemical

characteristics with previously observed toxicity patterns to estimate the potential risk of a new compound. In 2026, FDA announced acceptance of a letter of intent for an AI-driven digital liver model for DILI prediction under its ISTAND program, illustrating movement toward regulatory evaluation of such approaches.



11.7 Explainable and Trustworthy AI

Future toxicology models will need not only high predictive performance but also **interpretability, transparency and clearly defined contexts of use**. Explainable AI can help researchers understand which molecular or biological features contribute to a prediction. FDA's draft guidance on AI for regulatory decision-making emphasizes a risk-based assessment of model credibility for its specific context of use.

11.8 Integration of AI with New Approach Methodologies

The future is likely to involve integration of AI with **in silico, in vitro, organ-on-chip, omics and other New Approach Methodologies (NAMs)** rather than dependence on a single method. OECD's IATA framework describes the integration of multiple information sources to address toxicity questions and fill data gaps.

11.9 Regulatory Adoption and Standardisation

For AI-based toxicity prediction to become routinely useful in drug development, models require appropriate validation, reproducibility, transparency and defined applications.

Regulatory initiatives are already exploring how AI-driven tools and novel nonclinical methods can be evaluated for specific contexts of use. FDA's ISTAND program provides a pathway for qualification of certain innovative drug-development tools.

11.10 Future Perspective

Overall, the future of toxicology is likely to move from **generalised toxicity prediction toward mechanism-based and increasingly individualised risk assessment**. AI can connect chemical structures with toxicological, molecular and patient-related information, while advanced experimental systems can provide biological validation. However, prospective validation, data quality, model transparency and regulatory acceptance remain important requirements before these technologies can be broadly implemented.

Specific Indications / Applications

Future AI-driven toxicology area	Specific indication
Hepatotoxicity	Drug-induced liver injury (DILI) prediction
Cardiotoxicity	Prediction of drug-induced cardiac adverse effects
Nephrotoxicity	Prediction of kidney toxicity
Genotoxicity	Ames mutagenicity and related endpoints
Carcinogenicity	Early carcinogenicity-risk prediction
Personalised toxicology	Identification of individuals/populations with differential susceptibility
Toxicogenomics	Prediction using gene-expression and multi-omics signatures
IVIVE	Translation of in vitro toxicity results toward in vivo responses
Digital toxicology	Virtual biological/animal models and synthetic toxicity data
Precision drug safety	Individualised assessment of toxicity risk

The FDA's current **SafetAI** work specifically includes hepatotoxicity, carcinogenicity, mutagenicity, nephrotoxicity and cardiotoxicity, making these particularly relevant examples for this section.

12. CONCLUSION: Towards a Safer Digital Drug Discovery Pipeline

In silico toxicity screening is becoming an important component of modern drug discovery because it enables early, rapid and systematic identification of potential safety liabilities. Computational approaches such as QSAR, molecular modelling, machine learning, deep learning and read-across can support the prioritization of compounds before extensive experimental testing, thereby helping to reduce late-stage toxicity-related failures.

The future of drug safety assessment is likely to depend on the integration of in silico, in vitro and in vivo evidence rather than relying on a single method. Integrated approaches can combine computational predictions, experimental toxicity data, omics information and mechanistic knowledge to provide a more comprehensive assessment while reducing unnecessary animal testing.

However, computational predictions must be interpreted within their applicability domain and validated appropriately because data quality, biological complexity and model uncertainty can influence prediction accuracy. With advances in AI, human-relevant models and integrated testing strategies, in silico toxicology can contribute to a more efficient, predictive, ethical and safety-focused drug discovery pipeline.

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