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ORIGINAL RESEARCH ARTICLE

Artificial Intelligence in Predictive Toxicology: Modelling Xenobiotic Interactions and Human Risk Assessment

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ABSTRACT

Development of novel, rapid and robust approaches to toxicity screening has been accelerated by the expanding diversity of xenobiotics in pharmaceuticals, agriculture and industrial processes. The classical animal-based in vivo approach is slow, expensive and ethically restricted, thus stimulating the interest in the application of artificial intelligence (AI) as a data-powered technique to predict chemical hazards. Recent advances, challenges, and opportunities in this regard are reviewed here, focusing on achievements in machine learning (ML), deep learning (DL), quantitative structure–activity relationship (QSAR) modelling, omics-supported toxicity prediction, and the integration of these with physiologically based pharmacokinetic (PBPK) models. AI approaches can predict hepatotoxicity, carcinogenicity, endocrine disruption and multi-endpoint toxicity through high-dimensional chemical, biological and exposure data analysis. The use of these new tools to make predictions about the impact of chemical exposure in humans, using AI assisted PBPK modelling and toxicodynamic prediction can potentially assist risk assessors by increasing the accuracy with which internal dose may be predicted, allow for detection of vulnerable subpopulations or simply move us to a position where we are making decisions on data that puts prevention more proactively into action. The review also discusses present challenges with respect to data imbalance, low interpretability and variable data curation which hinder regulatory approval. Top emerging opportunities, including explainable AI, digital twins, and federated learning, have the potential to develop transparent, generalizable,

and ethically aligned toxicological frameworks. By translating methodological improvements to real-world challenges, this review adds input to the global picture for safer chemical design and sustainable risk governance progress, with support of SDG 3 (Good Health and Well-Being), SDG 12 (Responsible Consumption and Production), and SDG 13 (Climate Action).

Keywords: Artificial Intelligence, Predictive Toxicology; Xenobiotic Interactions; Machine Learning; Human Risk Assessment; SDG 3, SDG12, SDG13

1. Introduction

Toxicology as a discipline is transitioning from traditional wet bench experimentation to that in silico with computational modelling and the prediction of adverse outcomes. Given the explosion of both chemical diversity and environmental pollutants, knowledge on interferences by xenobiotics and their toxicological outcomes has emerged as topic of pressing concerns for public health and environment protection. Xenobiotics are artificial substances, such as drugs and pesticides, industrial chemicals, and environmental pollutants that are foreign to the biological system.

The emergence of AI enables new possibilities to predict and understand the complicated toxicological reasons for xenobiotics. The AI algorithms can perform analysis on large datasets produced from chemical, biological and clinical research studies that help to identify patterns of chemical structure-toxicity associations. AI-backed predictive toxicology, on the other hand, seeks to predict whether or not new compounds will be toxic before human (or environmental) exposure in order to minimize risks and overall reduce in vivo testing needs.

New advances in artificial intelligence are reshaping predictive toxicology by offering modern ways to analyses biochemical interactions and improve human toxicity prediction [1]. This review focuses on AI, including machine learning (ML) and deep learning (DL), applied across high-throughput data, drug metabolism, and excretion studies [2]. The widespread adoption of AI across scientific fields highlights its growing importance in toxicology and the need to integrate it into hazard assessment frameworks [3]. Toxicology has shifted from data-poor, empirical testing to data-rich environments, creating demand for AI tools capable of handling complex chemical and biological datasets [3]. These methods capture toxicological patterns and relationships that traditional techniques cannot resolve, improving the accuracy of toxicity predictions [3]. AI can process diverse information, including genomics and environmental signals, enabling deeper insights into toxicity mechanisms [3]. It is also positioned to address key challenges in risk assessment, such as interpreting complex data, assessing mixture toxicity, low-dose effects and accommodating New Approach Methodologies [4]. Growing polypharmacy and patient variability further expose limitations of classical toxicology, reinforcing the value of AI in drug safety evaluation [5]. ML techniques are now widely used in safety assessments, supported by high-throughput QSAR modelling and large integrated datasets [5, 6]. These tools enhance the prediction of xenobiotic effects and strengthen human health risk assessment by combining medical, chemical, and pharmacological data [5]. AI also supports early detection of toxicities, pathway analysis, and in vitro hepatotoxicity prediction, reducing late-stage failures in drug development [7–10]. Its efficiency, reduced reliance on animal testing and improved predictive power make AI a transformative force in modern toxicology [11–17].

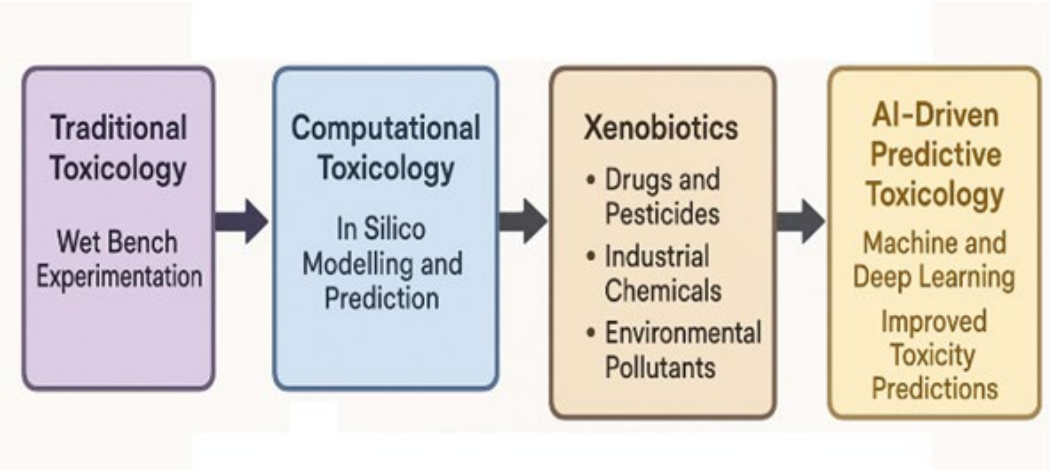

Figure 1. Transition from Traditional Toxicology to AI-Driven Predictive Toxicology

Figure 1 links the visual progression of the traditional toxicological approach towards computational AI-based predictive target organ-specific models to the principal argument developed within the introduction. The image shows how computational methodologies are transforming toxicity prediction, and the text describes why this transformation enables early identification of harmful compounds and reduces the need for experimental reliance. AI-based predictive toxicology models facilitate early detection of toxic compounds as well as in the selection of lower candidates, diminishing expenses that can be incurred from a late-stage failure in drug development [12]. These in silico tools, based on physicochemical properties, can then be used to generate toxicological information rapidly and at a reduced cost (i.e., new substances don't need testing or the use of animals) [18]. These architectures train on receptor ligand graphs and protein interaction data, learning complex SAR at the atom level that can be used for large-scale virtual screening against vast chemical space [19]. This method reduces the dependence on actual laboratory experimentation and speeds up new drug discovery pipelines [20]. Preclinically speaking, AI in combination with Organs-on-Chip and Digital Twins technologies has the potential to simulate human response allowing research be more efficient and socially responsible [21]. These approaches are consistent with green or sustainable toxicology principles that emphasize early detection and prevention of adverse outcomes through thoughtful design of chemicals [22]. AI also has high potential in drug toxicity prediction, as a number of ML tools have matched or even outperformed animal tests for multiple toxicity endpoints, hinting at possibility to substitute some traditional safety testing [9; 23]. Challenges still persist regarding the quality and diversity of training data and model complexity [11], although advancements in algorithms and curated toxicology databases have been improving model precision [24]. AI-guided hypothesis generation has proved to be of use in the field of cardiotoxicity, notably allowing omics and clinical data combination for overall predictions [25, 26]. These progress contribute to the mechanistic understanding of xenobiotic interactions and further human risk assessment [21]. AI is extended by expert systems, generative AI in assisting chemical risk assessment & decision support, documentation and regulatory communication [3].

The introduction explains the historical context of toxicology to now and the advent of AI-based approaches but does not however give a clear indication of what specific gap in this literature review seeks to fill. Machine learning, deep learning and QSAR were already listed in other recent reviews on AI in toxicology, so the manuscript should clarify what is missing today. The introduction ought to concisely state which weaknesses in the literature this article tries to address and why it provides a novel contribution—in terms of a wider synthesis, newer methodological understanding or understanding issues including integration of recent AI frameworks as relates studies on predictive toxicology.

2. Role of Artificial Intelligence in predictive toxicology

AI enhances predictive toxicology by mining chemical and biological information to identify patterns associated with toxicity. These models support nonlinear associations of the molecular features with toxicological responses, allowing to detect hazardous compounds at earlier time points and interpreting dose–response relationships more clearly. Chemical descriptors can be integrated with genomics, proteomics and metabolomics data leading to a more comprehensive understanding on pathway level mode of action disruptions causing toxicity [10], [12], [25], [27], [28].

2.1. Machine learning approaches

Descriptors, fingerprints or assay-based features are fed into machine learning algorithms like Random Forests (RF), Support Vector Machines (SVM), Gradient Boosting and k-Nearest Neighbors to predict the toxicological endpoints. These models cover different endpoints such as hepatotoxicity, carcinogenicity and neurotoxicity [24], [29], [30]. Ensemble methods enhance generalization by combining predictions of different learners, a feature that is helpful for complex endpoints like reproductive toxicity or carcinogenicity where no single model can be relied on to perform consistently [34–37].

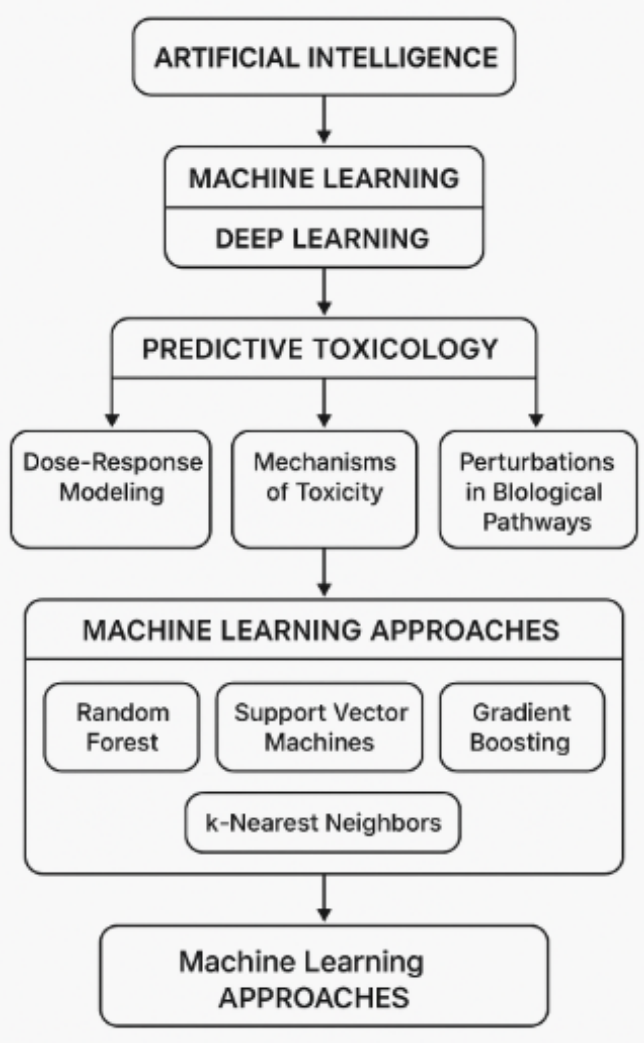

Figure 2. Role of Artificial Intelligence in Predictive Toxicology

Figure 2 explains the integration within the machine learning and deep learning section. The increased release illustrates how the schematic relates various AI approaches to toxicological tasks, like modeling dose–response behavior, detecting pathway disturbances and multi-endpoint toxicity prediction.

Table 1. Role of Artificial Intelligence in Predictive Toxicology

Section	AI Approach / Model	Description / Mechanism	Application in Toxicology
Role of AI in Predictive Toxicology	Machine Learning (ML) & Deep Learning (DL)	AI utilizes existing toxicological knowledge and identifies nonlinear relationships between variables; it predicts unseen compounds with accuracy.	Models dose-response effects, toxicity mechanisms, and biological pathway perturbations using genomics, proteomics, and metabolomics data.
Machine Learning Approaches	General ML models (RF, SVM, Gradient Boosting, kNN)	Based on chemical descriptors, fingerprints, or biological assays to predict endpoints like carcinogenicity, hepatotoxicity, neurotoxicity.	Applied for predicting toxicity endpoints across species.
Random Forest (RF)	Ensemble learning builds multiple decision trees and averages results.	Handles high-dimensional and nonlinear data effectively.	Used for classifying toxic vs. non-toxic compounds; substructure-based toxicity prediction.
Support Vector Machine (SVM)	Separates data with optimal hyperplanes in high-dimensional space.	Manages toxicogenomic datasets and molecular classification.	Used for distinguishing toxic and non-toxic chemicals.
Ensemble & Hybrid Models	Combines outputs of multiple base learners (RF, SVM, XGBoost, LightGBM).	Reduces bias and increases predictive accuracy.	Applied for complex endpoints like carcinogenicity, reproductive, and acute toxicity.

Table 1 explains the key roles of artificial intelligence techniques, including machine learning and deep learning, in predictive toxicology. It summarizes various models, their mechanisms, applications, and outcomes in identifying and assessing chemical toxicity with improved accuracy.

2.2. Deep learning models

Deep learning models further advance prediction power by learning features from raw observables including molecular images, SMILES strings, molecular graphs, and high-dimensional omics profiles. CNNs encode spatial and hierarchical molecular fingerprints, and the GNNs extract the structural anatomical connectivity with relevance to being able to detect significantly related toxicophoric [40],[46], captured at a lower resolution. Autoencoders aid in identifying hidden structures in omics data, while GANs support the generation of novel chemical designs with selectivity to toxicity [42], [45], [47], [48]. Multimodal deep learning models that integrate both chemical and biological information have been reported to improve multi-endpoint toxicity prediction [49], [11], [50].

Table 2. Deep Learning Models Applied in Predictive Toxicology

Deep Learning Model	Data Representation	Key Function in Toxicology	Advantages	Examples / Applications
Convolutional Neural Networks (CNNs)	2D or 3D molecular representation; molecular images	Identify toxicophores and activating structural motifs in molecules	Captures spatial and hierarchical features of molecules; learns from molecular structures without handcrafted features	Used to predict toxicity based on molecular imaging; supports toxicity classification and regression problems
Graph Neural Networks (GNNs)	Graph representation of molecules (atoms = nodes; bonds = edges)	Learns molecular connectivity and functional groups related to toxicity	Retains chemical structure information; interprets substructures causing toxicity; generates neural fingerprints	DeepTox and GCN-based systems used for toxicity prediction and multi-endpoint toxicological modeling
Autoencoders (AEs)	High-dimensional toxicogenomic and	Dimensionality reduction; discovery of	Handles unlabeled large-scale data;	Used in toxicogenomics for detecting hidden

Deep Learning Model	Data Representation	Key Function in Toxicology	Advantages	Examples / Applications
	omics data	latent factors linked to toxicity outcomes	identifies biomarkers and toxicity mechanisms	toxicity patterns and novel biomarkers
Generative Adversarial Networks (GANs)	Molecular structure data and toxicological profiles	Generation of new compounds with controlled toxicity	Enables safer chemical design; explores structure-activity relationships	Creates virtual chemicals with reduced toxicity profiles for drug discovery and environmental screening
Attention-based Chemical Language Models	SMILES strings and molecular text data	Learning complex chemical semantics and molecular relationships	Handles large chemical datasets with improved feature representation; interprets context-dependent molecular interactions	Chemical transformer models predicting toxicity across varied chemical spaces
Multi-task Deep Learning Models	Combined molecular and biological datasets	Predicts multiple toxicity endpoints simultaneously	Enhances generalization across diverse toxicity mechanisms; increases prediction accuracy	Used for predicting hepatotoxicity, mutagenicity, and multi-target toxicity from shared molecular features

Table 2. (*Continued*)

Table 2 summarizes the main deep learning models applied in predictive toxicology. Each framework handles chemical and biological data differently, improving prediction accuracy, interpretability, and discovery of toxicity mechanisms. These methods collectively support toxic compound identification, drug discovery, and environmental safety assessment.

3. Modelling xenobiotic interactions using AI

AI techniques can help model from molecular to system levels of xenobiotic interactions. Based on chemical structure, biological response and exposure information, AI can so be used to detect molecular initiating events, link adverse outcome pathways and make better estimates of dose–response behavior [50], [12]. Sophisticated models such as transformers can capture subtle structural relations, and predict toxicity effects with high accuracy in both aquatics and mammals without the need for in vivo data [51-54].

3.1. Quantitative Structure–Activity Relationship (QSAR) integration

AI-driven QSAR models establish links between structural traits and toxicological endpoints without pre-assumptions on how such links shall appear in flexible or nonlinear forms. Deep learning–based QSAR methods, such as graph convolutional models, enhance the generalization to multiple and structurally diverse chemical classes, and reinforce predictions on endpoints with a scarcity of experimental data. Moreover, these models include molecular docking and/or receptor binding data to improve the prediction for targets including PPARs, AhR, estrogen receptors [55], [56].

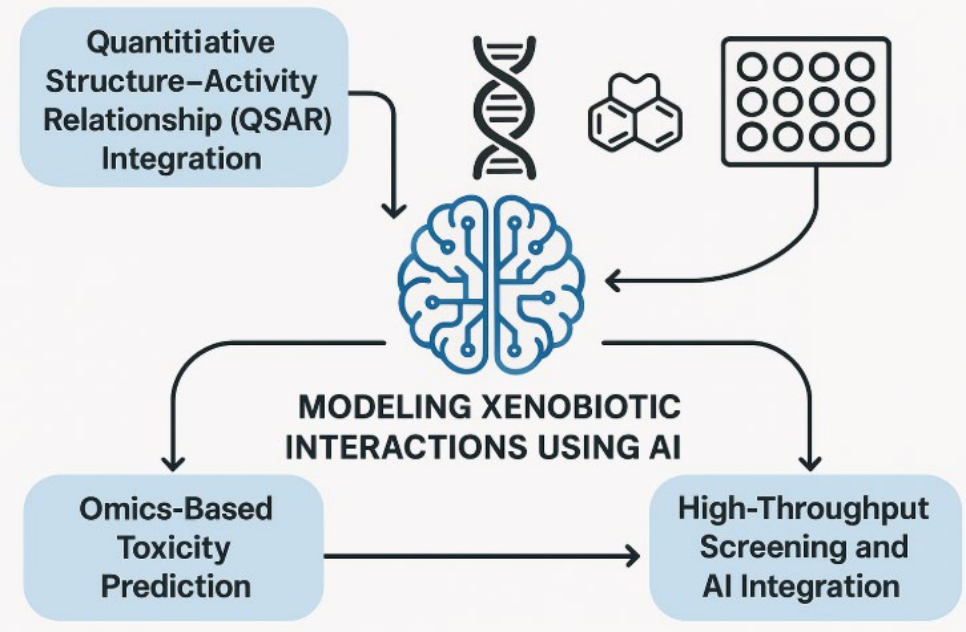

Figure 3. Modelling Xenobiotic Interactions Using Artificial Intelligence

3.2. Omics-based toxicity prediction

Integration of omics data using machine learning can be used to gain access to early molecular changes preceding organ toxicity. These models reveal exposure biomarkers, group compounds with expression profiles and facilitate mechanism investigation by linking to adverse outcome pathways. Integration of AI-omics has been used to evaluate genomic instability, endocrine disruption and other toxicity pathways that are central in human health risk assessment [57], [50], [58].

3.3. High-throughput screening and AI integration

High-throughput screening provides large chemical activity data sets that AI can analyze to find active compounds, interpret complex dose–response curves, and estimate toxicity potency. Deep learning leads to better feature extraction on the HTS assay outputs in order that harmful chemicals could be more quickly discovered and more reliably prioritized for regulatory tests [59], [49], [60]. Such integrated methods facilitate translation between in vitro screening and in vivo risk assessment [4].

Figure 3 shows the field of AI models xenobiotic interactions via three components: i) QSAR integration, ii) omics-based toxicity prediction and iii) high-throughput screening. Together, they allow for a comprehensive investigation of chemical patterns in behavior, toxicity modes and human health risks.

4. AI for human health risk assessment

Recent research is proving that AI models are actually transforming how we evaluate human health risk. These models have in some cases, surpassed results from animal experimentation when predicting both acute and chronic toxicity using machine learning systems based on Tox21, and high-throughput transcriptomics (HTT) data, leading to time-efficient and repeatable screening results. To improve internal dose and tissue concentration estimates, AI-aided PBPK models have been able to learn from various exposure datasets, further enhancing accuracy for chemicals with little in vivo data [61]. In cardiotoxicity AI has been used in the generation of hypotheses, where transcriptomic signatures associated to structural cardiac damage were recognized, allowing risk detection earlier than common experimental assays. Meanwhile, some AI applications have encountered application problems: Deep learning models for predicting hepatotoxicity perform well on the training data but are limited in their ability to adapt when facing new chemical space, mainly due to the insufficient diversity of data and weak interpretability. These examples illustrate the

progress and challenges associated with deploying AI for regulatory risk assessment, underscoring the need for more transparent models and improved datasets to achieve consistent performance across populations and exposure scenarios.

4.1. Toxicokinetic modelling

AI supports the PBPK modelling by predicting absorption, distribution, metabolism, and excretion (ADME) profiles. The TEED models, which are based on measurements of xenobiotic tissue exposure at different sampling sites and not solely on plasma concentration, allow prediction of the bioavailability and distribution in the body of the considered xenobiotics across several tissues with low experimental input. Hybrid AI-PBPK models improve the accuracy of predicting human variability as well as cross species extrapolation. These models are especially useful for estimating the internal doses of chemicals across life stages and populations, an important consideration in screening human health risk [62]. In addition, machine learning algorithms can be used to further optimize parameters inside PBPK models for better prediction performance and saved computational resources taking repeated long simulations into considerations [56]. This type of integration will provide a more representative estimate of the uncertainty contributed to exposure and dose predictions, ultimately leading to improved risk characterizations. Particularly for new substances, the need for predictive computational models that give input parameters values for PBPKs is growing, since standard data production is time-consuming and costly [63]. These AI-powered advancements also imply the potential for faster, more adaptable assessment of the safety profile of a chemical and earlier strategies to address any possible concerns. This type of probabilistic risk assessment such as perceives not only the predictions for individual endpoints, but also provides uncertainty estimates on how risky a specific prediction is(i.e., uncertainty in the outcome of assessment) which enable to move from deterministic toward more accurate about uncertain indicative models [28].

4.2. Toxicodynamic modelling

Mechanistic toxicodynamic models based on machine learning are able to describe dose–response relations and predict cellular responses induced by exposure with xenobiotics. AI can also comb through cell-line data as well as clinical findings, allowing it to work out what the critical dose thresholds are and calculate the probability of undesirable side-effects. This provides an opportunity to test compounds from which chronic toxicities or organic damage are anticipated. These kinds of models particularly when done in more than one species include a very useful source of information especially for the study and interpreting complex, multistep disease processes such as carcinogenesis or neurodegeneration where complex sequences of events lead to an adverse toxicological outcome [64]. Furthermore, AI supported toxicodynamic modelling might be able to include genetic and epigenetic factors of interindividual variability in response towards toxicants, thus moving toward personalized toxicology. Such predictive capabilities will be important to move towards proactive public health interventions, especially in the way of identifying at-risk populations where exposure reduction efforts can be taken [3]. However, while encouraging, interpretability is a challenge for complex deep learning methods and is not able to provide full explanations on model prediction making the use in regulated settings less prevalent [3]. Further research for better interpretability and transparency of such complex AI models that enable offering them up to regulatory review for human health risk assessment is needed [4]. Prospective Inference of Anonymized Patients' Risk Classification using Advanced Machine Learning Developed AI is a fast-developing field that has potential to radically change the manner in which risk predictions are made, from an empirical based discipline into a science driven by substantial data [3]. One of those transformations is enabled by the explosion of available massive data sets and advanced AI algorithms able to ingest, interpret, and learn from them in order to provide better and more-efficient risk assessments [3] [65].

4.3. Population-level risk assessment

Methods based on AI are being increasingly employed for population-based risk assessment a large scale. Demographic, genome and exposure information are input into the machine learning models to determine susceptibility and vulnerability to environmental toxicants. Applications of such strategies assist in early realization of susceptible populations and development of regulatory provisions for chemical safety. In addition, AI can be used to support the fusion between different real-world data, such as electronic health records and environmental sensor data, for supporting continuous monitoring and updating of population-based risk assessments. This could permit to implementation a more anticipatory and responsive public health monitoring, surpassing static risk evaluations, towards an estimation of actual risk under changing environmental context and population structure [69-79]. AI is invaluable for the prioritization of chemicals for further toxicological investigation and identification of new emerging environmental threats, as it can quickly screen extensive datasets [80-85]. For instance, advanced AI models have been developed to predict the toxicity of novel chemicals by comparing their structural features with those of known toxic compounds [86-90]. This capability is augmented by the use of AI in combination with high-throughput screening data and omics technologies to elucidate potential AOPs at a scale not previously achievable [91-98]. These developments may together enable faster and. more comprehensive chemical safety assessment, which might in turn support active risk management through early identification of hazardous chemicals [99-104]. This brings about moving from response-driven toxicology, where damage needs to happen in order for us to understand it, to predictive-based toxicology, which aims to predict and prevent bad things from happening [105-110]. Finally, AI models can integrate diverse sources of information (environmental monitoring data, clinical observations), presenting a holistic view on how xenobiotics interact with an organism and what is its effect on human health [111-119]. Such pool integration yields complex multifactorial exposures and patient susceptibilities, and translates into more reliable risk estimates [120-126].

Table 3. Artificial Intelligence for Human Health Risk Assessment

Model / Application	Focus Area	Key Function in Risk Assessment	Advantages / Contributions	Applications / Examples
Toxic kinetic Modelling	Physiologically Based Pharmacokinetic (PBPK) and ADME prediction	Predicts absorption, distribution, metabolism, and excretion (ADME) of xenobiotics; estimates internal dose and tissue concentrations	Enhances accuracy of internal dose predictions; supports cross-species extrapolation; integrates uncertainty estimation	Hybrid AI–PBPK models predict human variability, life-stage exposure, and tissue-level bioavailability with minimal experimental data
AI-Assisted PBPK Optimization	Parameter estimation and simulation acceleration	Machine learning refines PBPK parameters and reduces computational time	Enables probabilistic and real-time dose predictions; supports rapid screening of chemical safety	AI-accelerated PBPK modeling for parameter inference and risk quantification
Toxic dynamic Modelling	Cellular response and dose–response prediction	Establishes dose–response relationships; predicts toxic effects on cells and tissues	Identifies molecular events leading to chronic toxicity; supports early hazard identification	AI models predicting carcinogenic or neurotoxic effects; integration with gene and epigenetic data for personalized toxicology
AI-Based Risk Inference Systems	Personalized and population-level risk classification	Learns from clinical, genetic, and epidemiological datasets to classify individual risks	Enables proactive interventions and identification of at-risk groups	Machine learning–based systems for patient-specific health risk predictions
Population-Level Risk Assessment	Large-scale environmental and epidemiological data	Assesses susceptibility and exposure across populations	Integrates demographic, genomic, and environmental data	AI tools merging EHR and environmental sensor data for

Model / Application	Focus Area	Key Function in Risk Assessment	Advantages / Contributions	Applications / Examples
	fusion		for comprehensive population risk estimation	continuous monitoring and predictive health assessment
AI-Driven Chemical Prioritization	Chemical screening and toxicity prediction	Identifies and prioritizes new or emerging environmental threats	Supports regulatory decision-making and proactive chemical safety management	AI models comparing structural features of new chemicals with known toxicants; high-throughput screening integration

Table 3. (*Continued*)

Table 3 indicates the Role of AI in human health risk assessment at the toxic kinetic, toxic dynamic, and population levels. AI improves PBPK modelling to predict the internal exposure, promotes toxic dynamic modelling to interpret cellular and molecular risks, and enables population-based evaluation based on incorporation of real-world heterogeneous data. These frameworks allow for predictive, data-driven toxicology able to support safer chemical design and more efficient health risk management.

5. Challenges and ethical considerations

Despite these advances, the application of AI to predictive toxicology is limited by issues including data quality and transparency and interpretability of models. Sources of hazard data are often diverse, incomplete or biased within certain families of chemicals, which is a limitation to the generalization of the model. Additionally, the 'black-box' character of deep learning limits biological interpretability and regulatory acceptance. Ethical considerations exist in the data privacy, especially the use of human exposure or clinical data. More efforts are needed on transparent and responsible introduction of AI models into toxicological research, including the development of explainable AI (XAI) frameworks and standardized validation procedures. The increasing dependence on artificial intelligence in predictive toxicology comes with a number of technical, methodological and ethical challenges that must be addressed to ensure robustness, commitment and responsible application. These are mainly related to data availability, model explain ability, regulatory trust and the ethical treatment of human-related knowledge.

A more extensive review of the most recent studies indicates that the boundaries of predictive toxicology are then not just conceptual however seen in published models. Data imbalance is a long-standing problem in datasets like Tox21 and Tox Cast, where non-toxic samples are much more than the toxic classes. Some models trained on these datasets showed good performance in overall accuracy, but all of them failed to have strong sensitivity for minority toxic endpoints and thus missed many rare but clinically important effects like mitochondria toxicity or endocrine disruption. These results illustrate the bias introduced in performance and model robustness due to imbalance during new chemical testing.

The problem of interpretability is also encountered in deep learning–based QSAR and graph models, which often lead to highly predictive models that however offer limited interpretation on the molecular determinants of toxicity. Regulators in a number of studies observed that the uncertainty on the relationship between structure characteristics and output compromises trust in those models for decision-making. This gap illustrates the requirement for transparent methods and feature-level explanations particularly when scoring dictates safety assessments.

Data curation issues also affect the reproducibility of toxicity models. Studies which employ screening data available to the public reveal that loss of metadata and inconsistent assay nomenclature also importantly make for a less efficient application of trained models across multiple repositories. Such concerns highlight the importance of standardized data standards and detailed documentation for consistency between studies.

5.1. Data quality and bias

Toxicological data that are used to train AI models typically suffer from incompleteness, heterogeneity, or imbalance among classes of chemicals. Biases are introduced when the data collection protocols are inconsistent, certain compound categories may be underrepresented and also unbalanced dataset can cause biased predictions. No standard data formats and poor curations also limit model reproducibility. In addition, when there is bias in the training data, the prediction of toxicity may be misleading especially for new or less-represented chemical structures. Addressing these data disparities will require harmonized source repositories and high-quality annotations for the credibility of AI models.

5.2. Interpretable and transparent models

Many deep learning models work as a "black box," providing good predictive performance but little interpretability. This lack of transparency restricts the uptake of these approaches by toxicologists and regulators that require mechanistic information for risk assessment. When you do not know which features influence the prediction of a model, it is very hard to find out causative relations between molecular properties and toxic responses. Explainable AI (XAI) frameworks – techniques such as visualization tools and interpretable model architectures – will be necessary to close this gap in understanding and instil trust in the decision-making process conducted via an AI.

5.3. Privacy and ethical use of human information

As AI systems learn from and begin to operate using data collected on humans (including clinical and biomonitoring data) they are better able to project population level risks. Usage of such data raises distinct data privacy, informed consent and ethical issues. Storage and analysis of personal or sensitive biological data need to follow the data protection legislation and audit processes. Responsible oversight and transparent use of human data require ethical governance frameworks.

5.4. Validation and regulatory consideration

Despite the demonstration of numerous AI models or predictivity, its application in regulatory toxicology is under-explored. AI-enabled decision-making strategies also have to satisfy the regulatory requirements of rigorous validation procedures and reproducibility. And if you have models, you can't really compare with, well then, a formal safety use is out the door. There is a demand for academia, industry and regulatory agencies to make concerted efforts to standardize the validation of methods and foster cross-agency harmonization.

5.5. Values in automated decision making

As artificial intelligence tools begin to weigh in on chemical safety and drug development, the ethical dimensions of automated judgment will be furiously debated. Overreliance on algorithms rather than providing appropriate human oversight could result in errors or biased interpretations that might have public health implications. Maintaining a human in the loop guarantees accountability and context and an ethical review of decision making.

5.6. Environmental and social justice implications

The impact on society as a whole should be taken into account in AI-assisted toxicology. Data representation can introduce bias that conceals asthmatic sub-populations more sensitive to pollutants. Integrating social and environmental equity in to the application of AI-based toxicological screening for equitable risk stratification across demographics and regional geographies.

In summary, the ability of AI to transform predictive toxicology is huge, but responsible exploitation will depend on solving challenges around data quality, model explainability and ethical oversight.

Transparent, explainable, and validated AI frameworks supported by high ethical and regulatory standards will play a crucial role in achieving scientific robustness and social trust in AI-based toxicological research.

6. Future directions

Interpretable AI (XAI) will be required as regulatory bodies that demand models provide explanations for their predictions rise. Recently it has been demonstrated that while deep learning models achieve high levels of performance, they are not transparent enough to uncover which molecular substructures or omics features drive the toxic response. Methods like attention mechanisms and concept activation vectors, layer-wise relevance propagation have also been utilized in QSAR and GNN models to elucidate key decision-relevant toxicophoric. These methods could enable regulators to consider how and why a model identifies a compound as hepatotoxic or endocrine active, potentially advancing XAI from an aspirational necessity for model deployment in chemical screening.

Another field of interest are digital twins. Digital twin platforms were already widely applicable in preclinical research to mimic tissue-level activities in cardiotoxicity and fibrosis. Analogously for toxicology, virtual organisms based on PBPK models, omics signatures and mechanistic pathways may also be constructed. Such systems could be used to test scenarios such as the combined exposure of chemicals, inter- and intraspecies life-stage differences and genetic sensitivity would not need to rely on in vivo studies. There are practical hurdles to overcome, including the requirement of high-precision physiological data and standardized organ-specific models, but with early proof-of-concept illustrations digital twins have the potential to become a central tool for predictive toxicology.

Federated learning presents a potential response to the increasing impediments of data sharing. Toxicity data are also scattered across pharmaceutical companies, academic groups and regulatory bodies, but these organizations cannot release raw datasets because of confidentiality and privacy. Federated learning makes it possible to train collective AI models while keeping institution sensitive data local. Recent applications in other biomedical domains indicate that such models can provide similar accuracy with centralized training. In the context of toxicology, this implementation can enable rapid development of large, diverse models for hepatotoxicity or developmental toxicity to be created in a time sensitive and computationally secure environment.

7. Conclusion

Computational toxicology has dramatically been transformed by AI, offering more complex means to model xenobiotic interfaces and human hazards with extreme precision. Recent developments in machine learning, deep learning and QSAR modelling are reviewed to provide an integrated overview of AI's approaches to predictive toxicology. This manuscript has summarized work from omics-based approaches, from xenobiotic interaction modelling and AI assisted risk assessment that collectively enhances early toxicity detection, toxicological mechanistic understanding or cross-species prediction. It also takes into account evidence from novel disciplines such as digital twins and federated learning, providing insights on how these can revolutionize future toxicological assessments. By connecting the algorithmic advancement with real-life issues in data quality, interpretability as well as validation, it seeks to offer an integrated framework summarizing both what has been done and what remains open in AI-driven toxicology. This places the work as a reference point for researchers that would like to design more transparent, dependable and biologically motivated computational models.

The application of these methods can contribute to predicting adverse chemical effects and the mode of action and enhance support for regulatory decision making with less reliance on animal test by ML/DL algorithms. Advances on data integration, model interpretability and ethical governance will render AIT as a critical element in the broad arena of contemporary toxicology toward safer chemicals innovation and human

health protection. AI has become a powerful methodology for predictive toxicology in the 21st century and has redefined how xenobiotic exposures are evaluated for human risk. With the help of machine learning and deep learning models, researchers can now predict chemical toxicity with increased accuracy, read complex biological responses, and detect potential risks early in the development phase. AI-powered approaches have decreased reliance on animal models, enabling data-driven decision-making faster in the domains of drug discovery, environmental safety and regulatory science. By combining AI with omics data, high-throughput screening and "quantitative structure–activity relationship" modelling (application of certain computer-based techniques to predict the toxicity or ecotoxicity of a population) has made more accurate and efficient prediction for toxicities possible, promoting the ethical and sustainable development of toxicological assessment. In the future, explainable and transparent AI methods will be essential to gain confidence in automated toxicity risk evaluations. Integration of AI with digital twins, multi-omics platforms and organ-on-chip systems will improve human risk modelling and predict potential health effects for a wide range of exposure scenarios. With the further enhancement of data quality, interoperability and interpretability, genetic toxicology by AI will promote toxicology itself as a science and enhance public health protection through proactive prediction of harmful chemicals or developing safer chemicals for future generations.

Authors' Contributions

S. Manjula Gandhi contributed to the conceptual framing of the review, initial literature survey, and preparation of the first draft of the manuscript. **S. Sugumaran** worked on structuring the sections related to machine learning and deep learning techniques and assisted in refining the methodological discussion. **N. Alangudi Balaji** contributed to the review of omics-based toxicology studies, data interpretation, and manuscript editing. **Govindarajan Murali** supported the technical analysis related to PBPK modelling, figures, and scientific validation. **Amruta Kundalik Mule** assisted with the compilation of recent advances in toxicodynamic modelling and helped in organizing the tables. **Harish Velingkar** contributed to reviewing studies associated with chemical risk assessment and provided critical revisions for clarity and coherence. **Anant Sidhappa Kurhade** supervised the overall writing process, coordinated revisions, integrated contributions across sections, and finalized the manuscript. **Muralidhar Ingale** contributed to editing, verification of references, and technical improvements across all sections.

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Conflict of interest

The authors declare no conflict of interest

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Abbreviations

Abbreviation	Full Form
ADME	Absorption, Distribution, Metabolism, and Excretion
AI	Artificial Intelligence
AOP	Adverse Outcome Pathway
CNN	Convolutional Neural Network
DL	Deep Learning
DNN	Deep Neural Network
EDC	Endocrine Disrupting Compound
GAN	Generative Adversarial Network
GCN	Graph Convolutional Network
GNN	Graph Neural Network
HTS	High-Throughput Screening
kNN	k-Nearest Neighbors
ML	Machine Learning
NAMs	New Approach Methodologies
PBPK	Physiologically Based Pharmacokinetic Model
QSAR	Quantitative Structure–Activity Relationship
RF	Random Forest
RL	Reinforcement Learning
RNN	Recurrent Neural Network
SVM	Support Vector Machine
XAI	Explainable Artificial Intelligence