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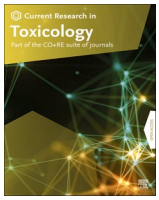

A Review of the Applications, Benefits, and Challenges of Generative AI for Sustainable Toxicology

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ABSTRACT

Sustainable toxicology is vital for living species and the environment because it guarantees the safety, efficacy, and regulatory compliance of drugs, treatments, vaccines, and chemicals in living organisms and the environment. Conventional toxicological methods often lack sustainability as they are costly, time-consuming, and sometimes inaccurate. It means delays in producing new drugs, vaccines, and treatments and understanding the adverse effects of the chemicals on the environment. To address these challenges, the healthcare sector must leverage the power of the Generative-AI (GenAI) paradigm. This paper aims to help understand how the healthcare field can be revolutionized in multiple ways by using GenAI to facilitate sustainable toxicological developments. This paper first reviews the present literature and identifies the possible classes of GenAI that can be applied to toxicology. A generalized and holistic visualization of various toxicological processes powered by GenAI is presented in tandem. The paper discussed toxicological risk assessment and management, spotlighting how global agencies and organizations are forming policies to standardize and regulate AI-related development, such as GenAI, in these fields. The paper identifies and discusses the advantages and challenges of GenAI in toxicology. Further, the paper outlines how GenAI empowers Conversational-AI, which will be critical for highly tailored toxicological solutions. This review will help to develop a comprehensive understanding of the impacts and future potential of GenAI in the field of toxicology. The knowledge gained can be applied to create sustainable GenAI applications for various problems in toxicology, ultimately benefiting our societies and the environment.

1. Introduction

Sustainable toxicology focuses on developing safe drugs, vaccines, chemicals, and treatments. It ensures minimum resource consumption and lowers toxic waste production, protecting living beings and the environment. As depicted in Fig. 1, fusing sustainability principles in toxicology aims to develop efficient and eco-friendly healthcare systems that improve public health and protect the environment, resulting in a prosperous society (Herzler et al., 2021; Crawford et al., 2017). On the other hand, the artificial intelligence application domain is growing fast. In this quest, Generative-AI (GenAI) can play a significant role. Classically, toxicology is a branch of science where the adverse effects of chemicals and their compounds on living organisms and the environment are analyzed and understood. Toxicology starts with observing and informing the abnormal symptoms, identification mechanisms, and expected treatments or solutions, which focus on flushing out toxins and minimizing any adverse effect on the health of the living organisms and environment. Toxicology can be divided into several subdisciplines: Clinical, Forensic, Environmental, and Industrial (Timbrell and Barile, 2023). Clinical toxicology and Forensic toxicology are more concerned with investigating deaths and health issues due to poisoning and pharmaceutical uses (Maurer, 1999). Further, Industrial toxicology analyzes the harmful effects of chemicals on workers in industries, workplaces, and offices. In particular, it focuses more on the manufacturing sector (Browning, 1944) and the last one, Environmental toxicology (Liu et al., 2023) which analyzes the adverse effect of chem

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and industrial processes on air and water and affects all living organisms.

During the last decade, it has been witnessed that Artificial Intelligence (AI) has grown significantly in several fields, including but not limited to robotics, healthcare, natural science, education, etc (Alam et al., 2024; Alam et al., 2019; Mehmood et al., 2017). Following similar patterns and realizing the numerous benefits today, AI-based technologies in toxicology are considerably increasing (Tetko et al., 2022). Over the last half-decade, the GenAI paradigm has been making news among users and the industry. However, the success of any technological paradigm depends not just on its applications but mainly on how the industry perceives it and public acceptance. GenAI has all these in its favor (Gartner, 2023; Wiles, 2023).

The GenAI paradigm is a class of AI models designed to generate new data by learning complex patterns and distributions from existing datasets. These models can address challenges in toxicology, including but not limited to data scarcity, anomaly detection, and the need for complex simulations. By generating synthetic datasets, predicting molecular interactions, and simulating chemical behaviors, GenAI has the potential to complement conventional toxicological methods. GenAI encompasses a variety of models, with the most widely used being Generative Adversarial Networks (GANs) and Variational Autoencoders (VAEs). Other prominent models include Transformers and Diffusion Models. Less commonly utilized approaches include Autoregressive Models, Normalizing Flows, and Energy-Based Models (EBMs).

GANs have two components: a generator and a discriminator. These two components function in cooperation. The generator produces new data points, and the discriminator checks whether the produced data is like training data. GANs can produce realistic synthetic data, which can help create toxicological datasets. VAEs are also used to generate data but are done differently. They first encode input data in a compressed form, creating new data by decoding compressed data. It enables anomaly detection and molecular feature exploration. (Gozalo-Brizuela et al., 2023). Transformers, widely used for natural language processing, use attention mechanisms. They process data sequences and help with text generation and multimodal content creation. Specifically, Transformers can analyze large-scale chemical datasets in toxicology and perform protein interaction modeling, which is critical in drug discovery and environmental toxicology. Further, they can predict protein structure and molecular properties (Lin et al., 2022). Diffusion models work by gradually corrupting data with noise. Then, learning reverses this process to generate realistic results. They are widely used in generating high-quality images and a udio, molecular simulations, and environmental risk assessment. These models can significantly address chemical toxicity prediction and sustainability-related toxicological challenges (Yang et al., 2023). Further, less widely used GenAI models, such as Autoregressive Models, Normalizing Flows, and Energy-Based Models (EBMs), make the GenAI model ecosystem diverse. Another AI paradigm in the limelight from early 2023 is Conversational-AI, which can engage, interact, and infer (Fu et al., 2022). One example is ChatGPT, the fusion of GenAI, which it interacts with users, and GenAI, which can generate content.

This review aims not to replace conventional toxicological techniques (Non-GenAI), which rely on statistics and classical machine learning, with GenAI. Instead, the paper emphasizes that these Non-GenAI can be enhanced and empowered by GenAI to drive sustainable advancements in toxicological research and development. Additionally, both branches can be seen as complementary rather than competitive in toxicology. We believe that the GenAI paradigms can play a critical role in developing an in-depth understanding of various aspects of toxicology. It has the power to revolutionize it and to have sustainable toxicological developments by saving time, cost, and resources. In this work, we discuss and understand how toxicology can take leverage from GenAI.

1.1. Research Aims and Contributions

To the best of our knowledge, no work has reviewed research and development work related to the possible applications of GenAI for sustainable toxicology. This paper aims to bring the research community's focus on how GenAI can benefit the toxicology field and help us enhance our understanding of it, ultimately benefiting our societies towards sustainable toxicological developments. The contributions of the paper are five-fold:

- To explain how and where GenAI can be applied in toxicology.
- To critically discuss each identified application of GenAI in toxicology.
- To compare holistically GenAI and non-GenAI methods, determine which outperforms the other and where they complement each other.
- To represent a generalized visualization of various toxicological processes powered by GenAI.
- To understand risk assessment and risk management in toxicology and GenAI-related developments.
- To understand how Conversational-AI can be empowered with GenAI in toxicology.

1.2. PRISMA Guidelines

The paper follows the PRISMA guidelines, and an extensive search was conducted across multiple academic databases, including Scopus, Google Scholar, IEEE, Elsevier, MDPI, Taylor and Francis, Springer, United Nations, etc., using search terms related to "GenAI," "Toxicology," "Drug Development," "Risk Assessment and Management," and "Applications of GenAI in Toxicology." The final selection criteria are

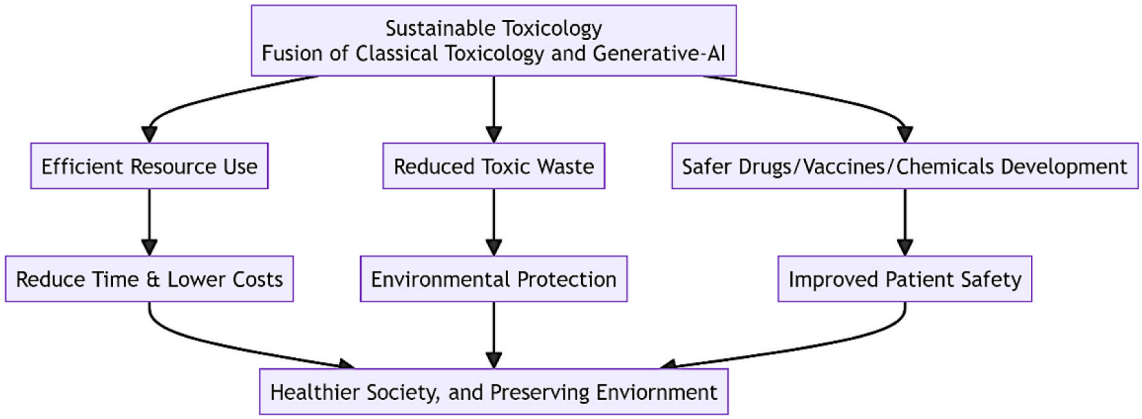

Fig. 1. Sustainable toxicology benefits.

based on recency and relevance, as depicted in Fig. 2. This search identified 371 journal papers, and 202 were selected for inclusion. Greater emphasis was placed on journal papers compared to conference papers, where 65 conference and proceedings papers were initially found, and 40 were included. Additionally, nine books are reviewed, of which five are included. Given the futuristic nature of the topic, crucial online news articles, technology companies, and whitepapers from reputable sources such as Forbes, BBC, Gartner, and McKinsey are also reviewed, resulting in 20 of the 57 online sources being cited. Reports from significant organizations like WHO and EPA are reviewed, and out of 27, 19 reports are included, focusing on the most relevant ones.

1.3. Paper Structure

The paper is divided into seven sections. Section 2 critically analyzes and discusses research and development work related to present and future applications of GenAI in toxicology. Section 3 critically presented a case study. Section 4 critically discusses risk assessment and management in toxicology, and Section 5 identifies possible benefits and challenges for GenAI in toxicology. Further, Section 6 addressed the empowerment of Conversational-AI using GenAI. Finally, the paper is concluded in Section 7. Fig. 3 depicts the high-level structure of the paper.

2. Applications of GenAI in Toxicology

−228600304139600GenAI is revolutionizing the world of creativity by producing real-like content and reasoning. It automates content generation and cost-effectively improves the variety of available content (La Salvia et al., 2022). Today, in almost all spheres of life, it has its applications. It is now used in finance for risk mitigation tasks and extracting hidden insights from financial data (Chui et al., 2023). In the manufacturing industry, it can enhance cohesion among the processes and facilitate product innovation (Wire and Generative, 2032). It holds significant importance in the automation, bio-sciences, and healthcare sectors, where applications of GenAI can obtain breakthroughs. Through personalized medicine, it can transform patient care forever (La Salvia et al., 2022; Saaran et al., 2020). The applications of GenAI in the field of toxicology are in their infancy. However, it possesses immense potential to transform toxicology. In Fig. 4, which is self-explanatory, the entire GenAI landscape is visualized holistically.

2.1. Data Generation

Data forms the basis of any experiment and methodology in toxicology. Experiments in toxicology are designed to collect data. Meanwhile, methods are developed based on the data they are dealing with. One of the main problems with toxicology is that data is often scarce and not readily available (Richarz, 2019; Pei et al., 2023). Also, data collection is time-consuming (Pei et al., 2023; Price et al., 2022) and complex (Sikakana and Roberts, 2020; Judson et al., 2008). Especially when we are collecting toxicological data, as chemical reactions and their visible effects can take significant time to appear so that they can be recorded. GenAI is better equipped than machine learning and classical deep learning techniques (Lu et al., 2023; Little et al., 2021). Over the last decade, considerable research and development work has occurred where artificial data is produced for toxicological analysis. GenAI has the potential to produce complex synthetic clinical trial data that speed up drug and treatment development, resulting in a faster and more accurate toxicological analysis. Krenmayr et al. (Krenmayr et al., 2022) proposed GANerAid for producing synthetic clinical trial data. Similar to (Krenmayr et al., 2022), Beigi et al. (Beigi et al., 2022) introduced Simulants, and Wang and Pai (Wang and Pai, 2023) fused GANs and SMOTE to produce small sets of structured clinical data. An exciting benefit of GenAI based synthetic data generation is that while sharing, we can preserve data privacy (Jadon and Kumar, 2023). Imtiaz et al. (Imtiaz et al., 2021) fused GANs with differential privacy to produce high-quality healthcare data.

Similarly, Dash et al. (Dash et al., 2020) produce a time series of patient medical data using a privacy preservation mechanism. From the above literature, a generalized step-wise explanation of how GenAI produces synthetic toxicology data is depicted in Fig. 5. It starts from initial inputs. Inputs can be random noise, latent space, and samples from latent space. The process ends at post-generation validation, which leads to the final synthetic dataset. This process may vary depending on the data generation problem researchers are dealing with. GenAI methods such as GANs and Variational Autoencoders can capture diversity in data. They can learn from unlabeled data and can impute missing data. Further, they can interpolate and imagine novel data examples. These characteristics place GenAI methods higher than other AI techniques, particularly in toxicology.

2.1.1. GenAI vs Non-GenAI in Data Generation

GenAI emerged as a potent tool for data generation that outperforms non-GenAI or conventional ML in this task. GenAI can produce complex

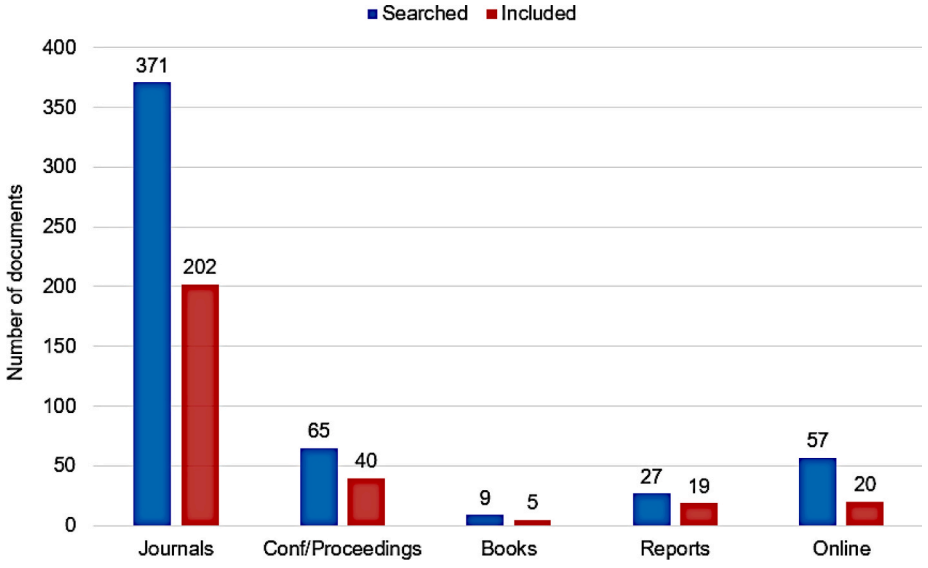

Fig. 2. Selection of references based on PRISMA.

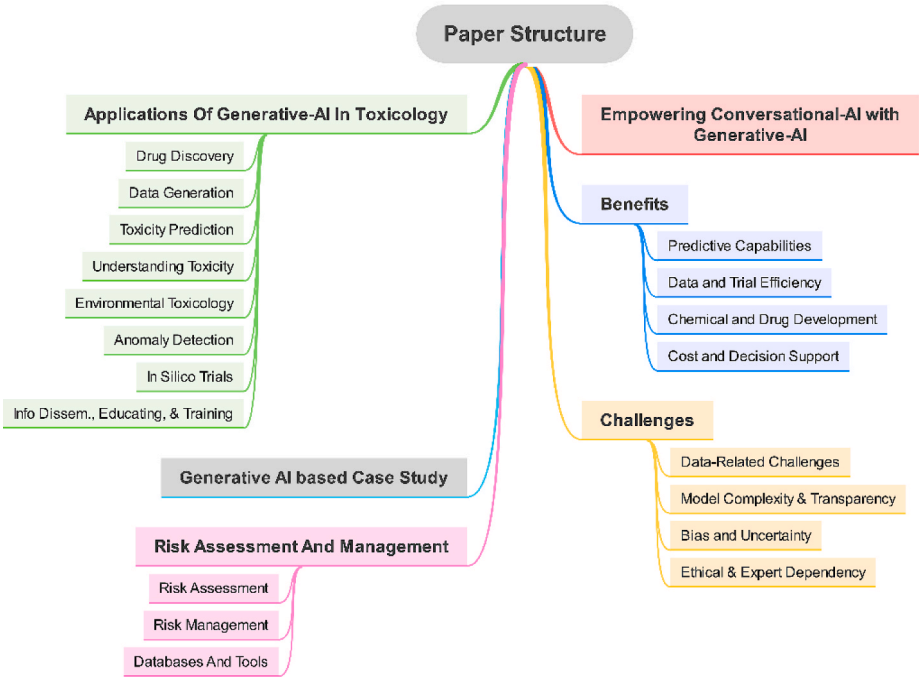

Fig. 3. Structure of the paper.

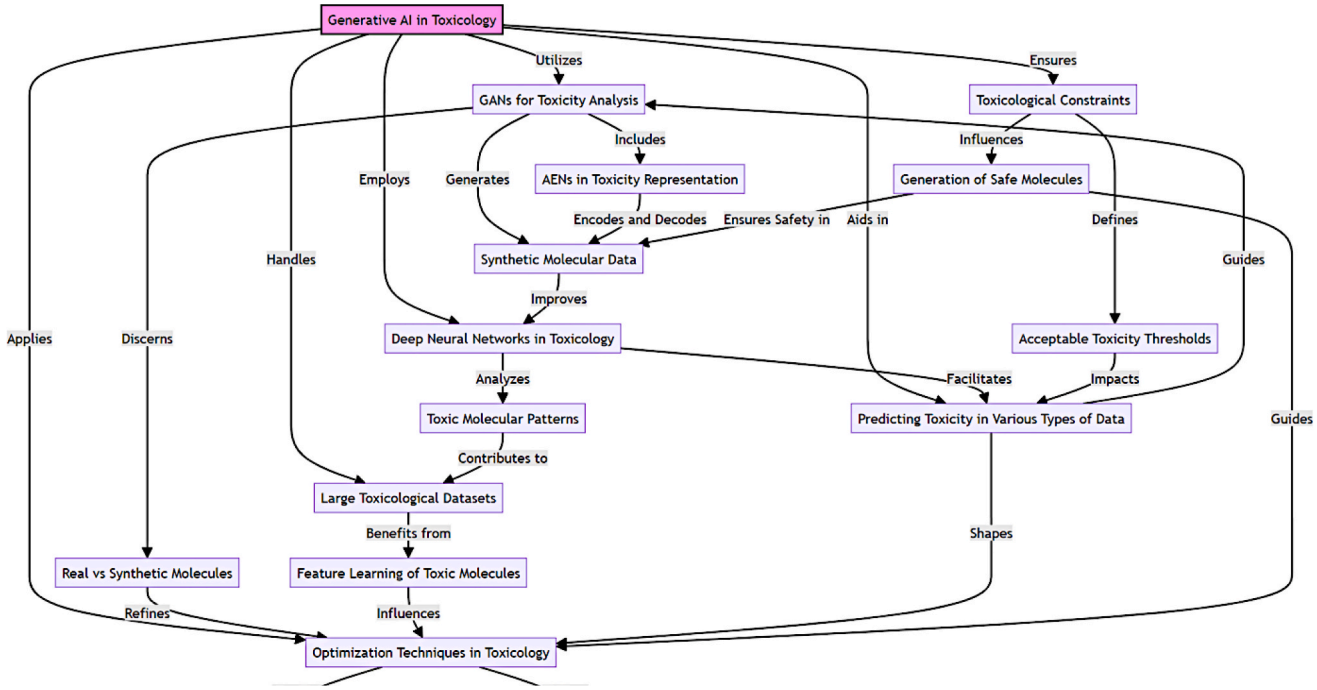

Fig. 4. Landscape of GenAI in the field of Toxicology.

distributions by understanding intricate relationships resembling real-world data, which is beyond the scope of QSAR models or ML. Additionally, GenAI can handle minority classes and augment imbalanced datasets, a task where conventional ML requires manual oversampling, which is less effective, especially when considering real-world variability. Another significant advantage of GenAI is its ability to fine-tune GenAI models specifically to produce targeted data, which is absent with non-GenAI. Moreover, GenAI can generate meaningful data representations even with limited labeled data. At the same time, ML fails to have sparse data availability.

Non-GenAI models' goal is predictive tasks and relies on existing data D, which consists of toxicological data like chemical properties and biological assays to create decision boundaries generally dependent on predefined transformations (Kevin, 2012; Christopher, 2006). Mathematically, the new data D' can be defined as:

$$D' = f(D, \theta, \tau)$$

Where the deterministic transformation function is denoted by f, further, model parameters and specific toxicological constraints such as regulatory thresholds and biological relevance are denoted by (θ, τ),

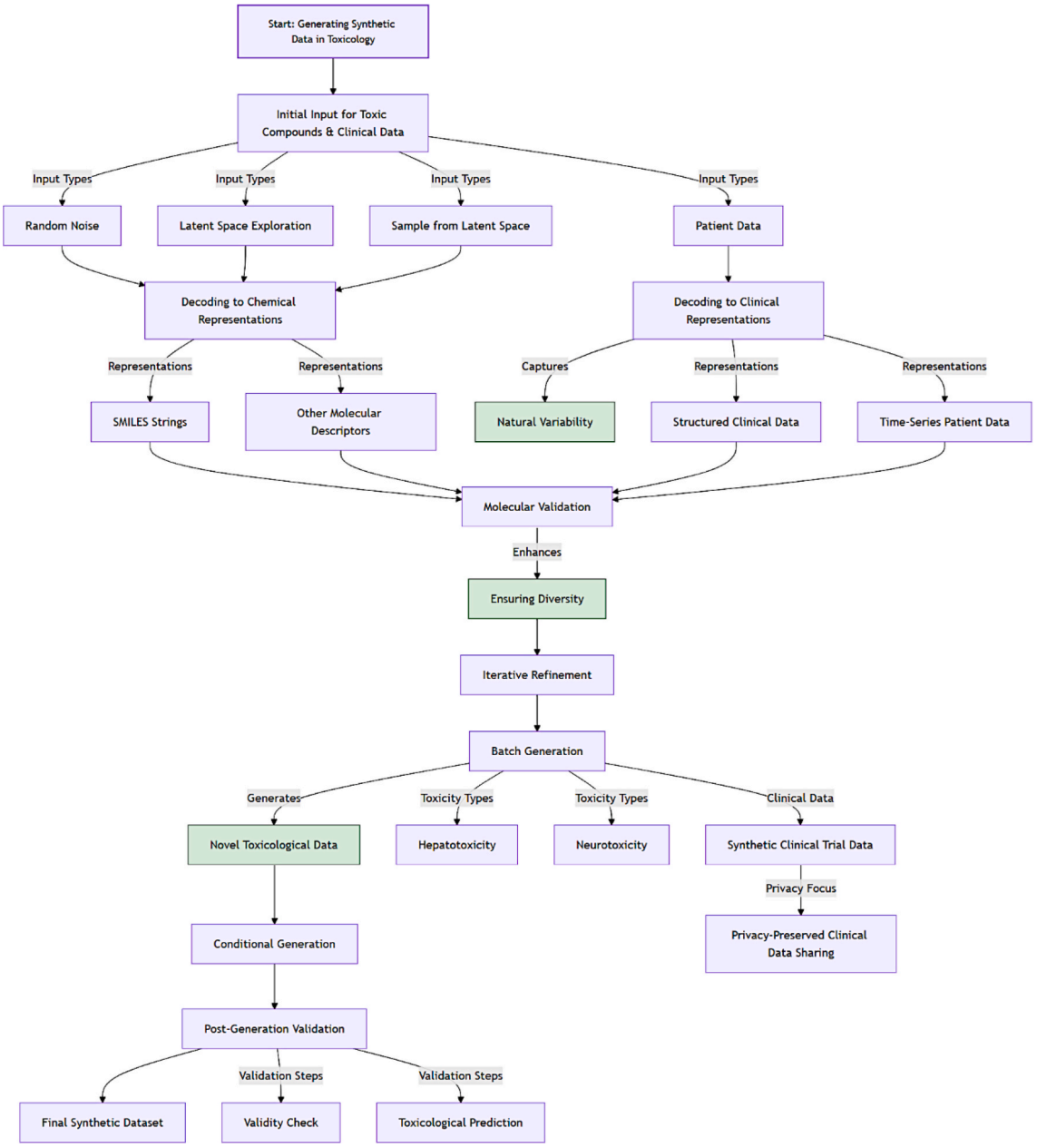

Fig. 5. Generalized explanation of how GenAI produces synthetic toxicology data.

respectively. Once trained, $f(D, \theta, \tau)$ is fixed, which means stochastic variations are not possible.

As a result, newly created data can only interpolate or extrapolate within D. This introduces several limitations in D'. This introduces several limitations in D' which includes limited diversity, lack of novelty, and inability to explore patterns beyond D.

Meanwhile, GenAI uses probabilistic and non-linear generation to create new data that is realistic, diverse, and domain-specific. Mathematically, data (G) produced by GenAI can be expressed as:

$$G = f(\mathscr{Z}, \delta, \tau), \mathscr{Z} \sim P(\mathscr{Z})$$

Where latent variable, model parameters, and specific toxicological constraints are denoted by $(\mathscr{Z}, \delta, \tau)$, respectively.

Unlike non-GenAI, GenAI does not require labeled data to generate new samples. The advantage GenAI is that latent variable $\mathscr{Z} \sim P(\mathscr{Z})$ enables GenAI models to create novel toxicological data that isn't present in D, which increases diversity (Kevin, 2012; Goodfellow et al., 2014). Also, as $\mathscr{Z}$ sampled from $P(\mathscr{Z})$, thus, natural variability is inherent. In conclusion, GenAI has better capabilities in creating new and novel data than non-GenAI.

2.2. Drug Discovery

Drug discovery is a branch of science that aims to discover new candidates for medications for diseases or medical conditions. It starts with the target (protein or a gene) identification and validations, chemical identification for the target, pre-clinical and clinical trials, and medical bodies' approvals. (Sadybekov and Katritch, 2023). Fig. 6 depicts GenAI in toxicology as a critical element of drug discovery processes. Today, machine learning and deep learning are used on a large scale to design safer drugs more quickly (Blaschke et al., 2020). Zeng et al. (Zeng et al., 2022) comprehensively discussed various conventional and modern-day AI methods used in drug discovery. The prime focus of Zeng et al. is on analyzing deep learning-based methods used in multiple drug discovery processes, such as molecule design,

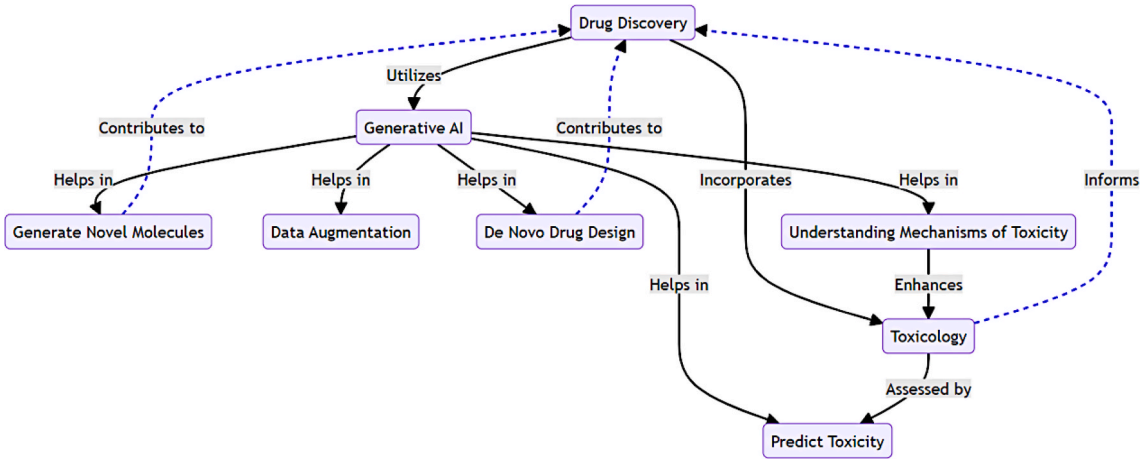

Fig. 6. Drug discovery and its relationship with GenAI.

understanding ligand–protein interactions, macromolecular drug design, therapeutic protein generation, etc. The following subsections highlight de novo drug design and in vivo trials as two significant aspects of drug discovery. Additionally, the role of GenAI in drug discovery, Post-Marketing Drug Surveillance (PMDS), Pharmacovigilance, and how GenAI complements Non-GenAI methods in drug discovery are discussed.

2.2.1. *Role of GenAI in Drug Discovery*

GenAI can potentially disturb these fields by enabling us to understand complex and highly non-linear interactions, chemical reactions, and the resultant toxicity of potential drugs (Martinelli, 2022; Craig, 2023). In the last decade, some attention has been paid to taking leverage from GenAI in the area of drug discovery. Novel performance measurement benchmarks for GenAI-based methods are needed. Preuer et al. (Preuer et al., 2018) proposed an evaluation metric focusing on GenAI models known as Fréchet ChemNet Distance in one such study. Quantitatively, it can present the diversity of generated molecules over actual molecules in terms of biological and chemical properties. Drug-like-molecule libraries contain trillions of compounds, but only a fraction can be synthesized and screened in labs. Predicting and modifying molecules' absorption, distribution, metabolism, excretion, and Toxicity (ADMET) characteristics are challenging. Tang et al. (Tang et al., 2021) showed that GenAI, combined with Reinforcement learning models, enhances the performance of GenAI models. Successful In silico Medicine's use of reinforcement learning is a faster and more focused technique for creating candidates for drugs with particular properties.

2.2.2. *De novo Drug Design*

De novo drug design is a technique where we create new drug molecules from zero. There is no dependence on existing drugs or chemical compounds. Significant computation and critical data analysis in the chemical domain are needed to design new drugs that can hunt their biological targets (Wang et al., 2022). Tong et al. (Tong et al., 2021) critically analyzed and discussed various generative methods and AI-based tools available for de novo drug design and examined the different performance evaluation benchmarks for GenAI methods. Kadurin et al. (Kadurin et al., 2017) proposed a progressive generative adversarial autoencoder method, druGAN, for designing de novo with specific properties. Grisoni et al. (Grisoni, 2023) proposed a de novo drug design method: a fusion of GenAI and on-chip synthesis. However, despite some cutting-edge studies, there remain challenges for GenAI in drug discovery. One bottleneck is that molecules can be designed using GenAI models with specific characteristics, albeit with high prediction accuracy, and updating properties of AD-MET is still challenging. Data scarcity and quality are other significant issues while training GenAI models. One critical challenge for GenAI in drug discovery is how to meet a perfect balance between feasibility and novelty. How to address legal and ethical concerns is also a significant issue (Grisoni, 2023; Mouchlis et al., 2021). Fig. 7, self-explanatory, depicts how the drug discovery process starts and where GenAI comes into the picture. The

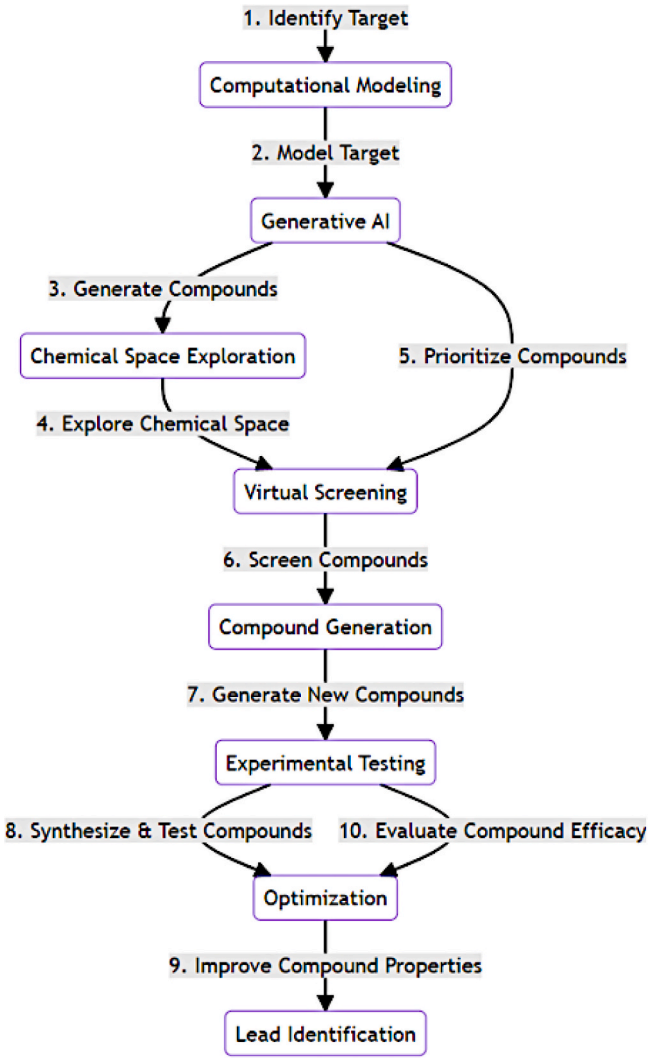

Fig. 7. A GenAI-based De novo drug design process.

potential of GenAI needs to be understood and exploited while keeping in mind the limitations of this paradigm.

2.2.3. In Silico Trials for Drug Development

In silico trials play a critical role in drug discovery, and it is basically computer simulations that help develop medical cures, including new drugs, biomarkers, medical devices, and new or improved therapeutic methods. Further, they also help to evaluate the treatment. Here, the potential performance of medical interventions is simulated and analyzed, including their safety and efficacy. In silico trials are faster than classical trials, cost-effective, and flexible (Kadurin et al., 2017). They are also safer as any adverse effect happens in a virtual world, not on real living beings. Ethics also reduces animal cruelty and human hardships in silico trials (Moradi et al., 2022; Badano, 2021). AI plays a vital role in conducting optimally designed simulations in this area. GenAI is making in-roads in this field now as it has the upper hand over other AI methods due to its ability to simulate cases and generate quality data, which is vital (Wang et al., 2022). In their work, Blanchard et al. (Blanchard et al., 2021) successfully used GANs to identify and improve new chemical space, leading to improved medicines and treatments. Another such work by Galbusera et al. (Galbusera et al., 2018) produced Spine's credible synthetic radiological images for using GANs. This eliminates the harmful effect of X-rays and other scans on the human body. One of the recent GenAI-based drugs entered from In silico trials and moved to human trials by biotech startups Exscientia (Wakefield and Medicine, 2023) and Insilico Medicine (Field, 2023). Due to this, human trials will be fast and highly safe as GenAI already simulates significant safety concerns. Even GenAI-based In silico trials have led to more rapid development of vaccines and highly potent vaccines with minimal side effects (ABSCI, 2023). The covid-19 pandemic hints at how AI-based In silico trials can revolutionize drug treatment development and our pandemic response, potentially saving many human lives (ABSCI, 2023; Matsuzaka and Yashiro, 2023). However, despite various advantages of generative, particularly in silico trials, it faces challenges that need to be overcome to exploit its full potential, as depicted in Fig. 8.

2.2.4. Post-Marketing Drug Surveillance (PMDS) and Pharmacovigilance

After the drug is launched in the market, we must keep iterating (Mohs and Greig, 2017), depending on post-marketing drug surveillance (PMDS) (Raj et al., 2019), a critical part of Pharmacovigilance where we monitor the adverse effects of the drugs (Khan et al., 2023). On the other side, well-developed statistical and conventional machine learning-based methods are available today to analyze structured data in healthcare (Rajula et al., 2020). However, approximately 80 % of healthcare data is unstructured (Kong, 2019; Sedlakova et al., 2023), consisting of text, signals, and images. Particularly in PMDS, most data sources are unstructured data, such as adverse event reports (FDA, 2023), social media (Powell et al., 2016; Yang et al., 2021), Internet forums (Kürzinger et al., 2018; Dirkson et al., 2022), medical literature (Carson and Strom, 1986), and spontaneous reporting systems (Alomar et al., 2020). Further, signal (safety concerns) detection is used in PMDS, which assists in monitoring and medical interventions. Signal detection utilizes data from social media and internet forums dealing with underreporting in PMDS (Kürzinger et al., 2018). Ibrahim et al. (Ibrahim et al., 2021) discussed informatics-driven signal detection approaches, including.

GenAI can be seen as a powerful tool for various natural language processing (NLP) tasks, as discussed by Yenduri et al. (Yenduri et al., 2023) involving unstructured data, and the same can be applied to Pharmacovigilance problems. In their review, Liang et al. (Liang et al., 2022) critically discussed AI technology in pharmacovigilance, including designing AI-based Pharmacovigilance solutions in resource-limited environments. In Pharmacovigilance, PMDS faces challenges like underreporting and data deficiencies, which means the chances of erroneous decisions are higher due to limited information. Praveen (Praveen, 2023) explores how integrating GenAI and human experts can improve drug safety monitoring and eventually empower Pharmacovigilance. GenAI application in post-marketing drug surveillance improves drug discovery by dynamic monitoring, personalized medicine, assisting drug repurposing, trend prediction, and implementing regulatory compliance. This empowerment of drug development processes by GenAI leads to safer, more effective, and efficiently developed drugs.

2.2.5. GenAI vs over Non-GenAI in Drug Discovery

As discussed in Section 2.1, GenAI excels in creating new data. This means that during the process of drug discovery, it can help in the creation of novel molecular structures, which mainly help in hit discovery, lead optimization, and molecular design. Further, creating new drug-like compounds helps overcome data scarcity issues and shorten

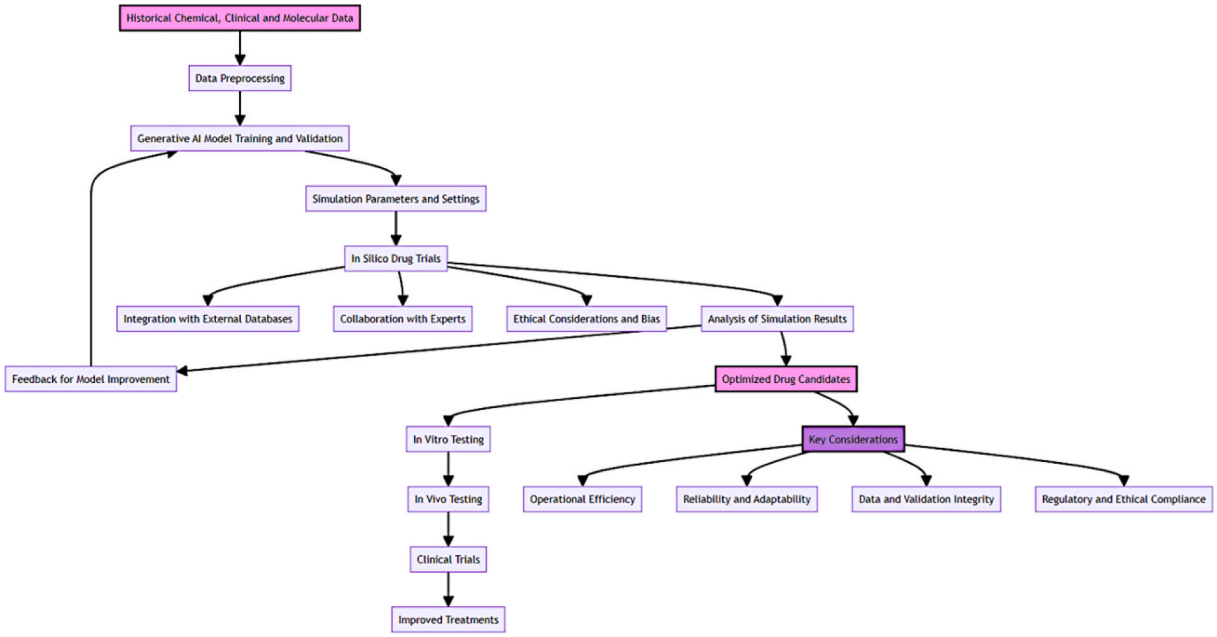

Fig. 8. GenAI landscape concerning In silico trials.

the de novo drug design, as discussed above.

However, despite various advantages, GenAI is here to complement non-GenAI rather than replace it. Both individuals are better in some drug discovery processes, as it is not a single process but a fusion of several methods focused on various computational, experimental, and clinical processes that work towards a unified goal. For example, Non-GenAI remains superior, computationally efficient, and preferred for ADMET predictive tasks, biomarker discovery, and virtual screening (Kamya et al., 2024; Visan and Negut, 2024). There are some critical reasons for this. ADMET properties depend on well-established experimental datasets such as ChEMBL, ToxCast, and PubChem. Non-GenAI models like SVM, Random Forests, Decision Forests, Deep Learning, and Gradient Boosting algorithms are trained to deduce relationships between molecular features and ADMET properties accurately.

Meanwhile, GenAI is not inherently designed to predict new molecules' pharmacokinetics. FDA and EMA prefer interpretable, deterministic models for regulatory acceptance rather than black box-based models like GenAI (Pyke, 2024; FDA, 2025). Quantitative Structure-Activity Relationship (QSAR) models are compelling in examining compounds' structural similarities, resulting in highly accurate predictions of molecular properties (Bastikar et al., 2022).

In Biomarker discovery (Pepe Escobar: Trump CORNERED as Putin, , 2025; Nguyen, 2024), feature selection and importance play critical roles. Non-GenAI provides explainability as it can help rank the most relevant biomarkers. GenAI can simulate synthetic biomarkers. However, it cannot offer strong biological relevance, and artificial data bias is risky if it depends entirely on it. GenAI can complement Non-GenAI in virtual screening by generating novel molecular structures (Zhou et al., 2024; Adeshina et al., 2020). However, it is weak in predicting binding affinity, which results in a high false positive rate and increased computational cost. Non-GenAI, or ML-based models, are the preferred choice in predicting interactions, ranking molecules based on real-world data, and aiding regulatory compliance. The hybrid solution is a better approach for virtual screening, where GenAI creates molecules and Non-GenAI filters and validates them. In summary, drug discovery can harness the strengths of both GenAI and Non-GenAI, empowering an efficient, data-driven, and targeted drug discovery process.

2.3. Predicting Toxicity

Predicting the toxicity of chemicals and compounds plays a crucial role in developing better drugs and minimizing the effects of toxins on humans and our environment. Adhering to the 3R principle is critical in reducing toxicity effects, particularly in animals. The 3Rs principle (Hubrecht and Carter, 2019) aims to implement moral and ethical aspects in using animals in testing products and research experiments. 3R synonymy is used to Replace, Reduce, and Refine. Replace means the approaches that substitute the use of animals in testing products and research. Reduce aims to minimize the use of animals in experiments where it is unavoidable. Refine seeks to reduce the pain and suffering of animals and focuses on animal welfare.

Understanding how chemical compounds affect the environment and living organisms is critical. To address this aspect, Li et al. (Li et al., 2022) analyzed QSAR and iQCCR modeling to understand carcinogenicity in aromatic hydrocarbons, minimizing animal testing and chemical synthesis. A paper by Li et al. (Li et al., 2022) aligned with the "Replace" aspect of the 3Rswhere computational models that can replace the vivo testing on animals are used. Meanwhile, Hao et al. (Hao et al., 2022) used advanced classification models for the environmental toxicity risk analysis of nitroaromatic compounds, which adheres to the "Reduce" aspect by reducing the number of animals required for the test. Another paper by Hao et al.(Hao et al., 2020) introduced a QSTR model to analyze the in vivo toxicity of nitroaromatic compounds in rats, which focused on relating an interspecies toxicity relationship. This work stresses the "Refine" aspect of the 3R principle as it focuses on minimizing the harmful nature of tests and concentrates on more humane approaches. Further, Chen et al. (Chen et al., 2023) analyzed the QSAR relationship between fused/non-fused polycyclic aromatic hydrocarbons (FNFPAHs) and their aquatic toxicity. This paper focused on the marine environment risk assessment and regulations related to fused/non-fused polycyclic aromatic hydrocarbons (FNFPAHs) contamination. Work (Chen et al., 2023) exemplifies all three Rs. by replacing the need for animal testing, reducing the number of animals needed, and refining the testing with the help of non-animal-based methodologies. A significant aspect Schmeisser et al. (Schmeisser et al., 2023) highlighted is that QSAR risk assessment prediction models are consistently enhanced by New Approach Methodologies (NAMs), which align with the 3Rs principles of animal testing, and these methods are crucial to transforming regulatory developments, which is the critical pillar of Next Generation Risk Assessment (NGRA).

GenAI can potentially revolutionize toxicity prediction for drugs, vaccines, and other materials (Badwan et al., 2023; Lin and Chou, 2022). However, not used much in this domain. Some works existed, such as Green et al. (Green et al., 2021) use embryonic zebrafish data to train deep neural networks and conditional generative adversarial networks (cGAN) to predict the toxicity of untested chemicals. This fusion improved prediction accuracy and other parameters like standard error, Kappa, and AUC, and it can be used as a prescreening tool for high-throughput toxicity testing. In another study, Zhan et al. (Zhan et al., 2022) predicted the radiation therapy toxicity level in the human body using Mc-GAN, a multi-constraint dose prediction model powered by GAN. The reasons for better prediction of Mc-GAN are that it uses an embedded UNet-like structure and dual attention module (DAM). Prior helps capture global and local data points, and the latter concentrates on internal semantic relevance. Two extra loss functions are used to further enhance accuracy in Mc-GAN. Schwalbe-Koda and Gómez-Bombarelli (Schwalbe-Koda and Gómez-Bombarelli, 2020) designed chemicals automatically while considering their toxicity nature using deep generative models. Interestingly, Huang et al. (Huang et al., 2016) dig into the sphere of machine learning models to handle the Tox21 challenge of predicting the toxicity of drugs and chemicals. This challenge aims to deduce how exposure to these sub-stances affects receptor and stress response pathways. Regardless of some initial developments, the toxicology community hasn't been much focused on using it.

2.3.1. GenAI vs Non-GenAI in Prediction

Despite several advantages, GenAI is in its infancy in toxicological prediction as it faces multiple challenges and is not yet the preferred choice for experts (Grisoni, 2023; Tan et al., 2023). Data quality and availability are one major challenge. The accuracy and robustness of any AI-based prediction in toxicity model depend on the quality and availability (volume) of data on which these models are trained, as identified in several studies (Guo et al., 2023; Cavasotto and Scardino, 2022; Pérez Santín et al., 2021). GenAI needs large volumes of high-quality and diverse data to create realistic molecular structures and predict toxicity. However, toxicity datasets generally have small datasets, class imbalance, and missing values that limit GenAI capabilities, struggle, and lack reliability in predictive tasks. However, non-GenAI models, such as QSAR, SVM, GBM, RF, etc., can produce high accuracies with smaller datasets due to feature engineering and explicit rules.

Interpretability refers to how well a model can be understood and how the model can explain its prediction decisions. This is important in regulatory organizations for toxicology, which needs solid reasoning and justification of decisions, as stated by Jia et al. (Jia et al., 2023). Non-GenAI models like Decision Tress, QSAR, etc., are inherently interpretable, which makes them a natural choice for prediction in toxicology. Non-GenAI models depend on explicitly defined features such as chemical fingerprints, molecular descriptors, and toxicity pathways (Walter et al., 2024). Regulating bodies prefer AI models, which support interpretability. GenAI models such as GANs, VAEs, and Transformers are black box methods where particular decisions are hidden in complex learning representations (Schneider, 2024). Further,

latent spaces make it more challenging to understand the decision-making process. Though some efforts have been made, however, they are pretty limited.

Validation is essential, especially in toxicology, as it guarantees that model results align with real-world experimental data (Guo et al., 2023; Basile et al., 2019). Non-GenAI models such as QSAR and classical ML use structured and thoroughly validated datasets, which facilitates explicit comparison of prediction results with actual dependent variables. Whereas GenAI models are good at creating novel molecular structures, no real-world verification exists. As no implicit proofs for these newly created molecular structures bring new challenges (Hartung and Kleinstreuer, 2025), validating predictions becomes significant. Additionally, a well-established fact about GenAI models is that their predictions are highly uncertain, as discussed in various works (Abou Hajal and Al Meslamani, 2024; Tonoyan and Siraki, 2024; Wittwehr et al., 2020), further complicating validation efforts.

Generalizability quantifies how well a model performs on unseen data, which is critical (Guo et al., 2023). Non-GenAI models use structured data, which means they can generalize well in cases where unseen data is within the limits of class boundaries. However, they may struggle when a completely novel data instance is an input. GenAI has an issue with overfitting during training, which can lead to poor prediction accuracy with unseen data (Abou Hajal and Al Meslamani, 2024). Thus, it confined the GenAI model to provide a reliable solution. Bias in toxicity arises due to imbalanced datasets. It can also be due to chemical representations or structural limitations (Tonoyan and Siraki, 2024). GenAI naturally inherits biases during the training process, as stated by Wittwehr et al. (Wittwehr et al., 2020). It can mean it is more inclined towards a specific molecular structure, giving unfair advantages over others during toxicity predictions (Zhou et al., 2024). It can have serious consequences in risk assessment and can affect regulatory decisions. Non-GenAI uses manual model tuning and weighting, which help remove or minimize biases (Tavares and Ferrara, 2024). This is also why regularity bodies have more trust in Non-GenAI models.

Additionally, computation resource requirements in GenAI and Non-GenAI bring the cost factor into play, which is critical as the industry needs accurate and cost-effective solutions in toxicity prediction (Hong, 2023). Non-GenAI models, such as QSAR, SVM, KNN, Decision Trees, etc., are predominantly white boxes and not deep, so their computational resource requirements are not too high. However, in GenAI models like GANs, VAE, Transformers, and Diffusion Models, the architecture is a complex, deep, black box and needs a significant amount of (GPUs, TPUs, memory, and power). One major issue is the billions of parameters these models use, significantly increasing complexity and computation cost (Appenzeller et al., 2024). Therefore, Non-GenAI methods are a more practical selection for world toxicology applications. With ongoing advancements, it is expected that GenAI models will be simpler, the number of parameters will decrease, and these models will be somewhat more explainable, eventually resulting in broader adoption of this paradigm for toxicity prediction.

2.4. Understanding Toxicity

An in-depth understanding of toxicology is vital for protecting human health and saving environmental damage (Stanek et al., 2011; Rivetti et al., 2020). Thalidomide (Vargesson, 2015), Vioxx (Krumholz et al., 2007), Fen-Phen (MIT, 1998), and Ranitidine (Food, 2023) are some drugs that were introduced as per analyzed benefits but were later found to have some toxic effects on human bodies. GenAI can enhance and simplify the understanding of toxicity to a newer level to detect the possible adverse effects of drugs, chemicals, and treatment at early stages. Therefore, it avoids health crises like (Jadon and Kumar, 2023; Imtiaz et al., 2021; Dash et al., 2020; Hubrecht and Carter, 2019) in future developments. Now, the critical question is how? In the following sub-sections, we're going to discuss the above.

2.4.1. Feature Selection

Machine learning applications in computing feature selection already play a critical role in the medical and drug discovery domain, as stated in a comprehensive analysis by Koras et al. (Koras et al., 2020) and Remeseiro and Bolon-Canedo (Remeseiro and Bolon-Canedo, 2019). The field hasn't been explored much where the GenAI model can be applied to compute feature importance, leading to feature selection (Alauthman et al., 2023). Toxicology is complex and often misunderstood, and later, after years, we figure out how many lives are affected by misunderstanding the toxicity of a drug or a chemical. Humans have diverse and complex structures of interconnection entities and their dependencies on each other. It is challenging to select a particular biomarker to identify toxin exposure (Zhavoronkov, 2018). Feature selection powered by GenAI can help determine optimal biomarkers, which can help identify exposure to certain toxins (Nair et al., 2023). Loads of feature selection methods are already there. However, GenAI has an edge over machine learning and other deep learning methods from two perspectives. Firstly, GenAI can create its data, improving the feature importance accuracy, as Liu et al. showed (Liu et al., 2021). Secondly, as analyzed in (Takyar, 2023; [125]) is more likely to interpret better complex relationships between various features and their effect on response variables. We can leverage feature selection to find critical factors, such as biomarkers and molecular descriptors, to enhance the understanding of toxicity mechanisms. Further feature selection using GenAI can improve the accuracy of Quantitative Structure-Activity Relationship (QSAR) models, which predict the toxicity of various compounds (Soares et al., 2022; Mao et al., 2021). However, not much attention has been given to this area. Today's and future toxicological data will be big data, and robust feature selection using GenAI can reduce dataset dimensions and enhance understanding of underlying processes. Computational complexity, training data, black-box approach, and model instability are challenges for GenAI based feature selection. However, numerous advantages include learning from non-linear and complex distributions, creating synthetic features unsupervised, and managing missing data points.

2.4.2. Latent Space Exploration

GenAI helps in Latent space exploration or Latent Toxicological Representation. It helps analyze intra-feature interactions and factors influencing them, which is necessary to understand toxicity (Fernandes et al., 2020). It can be defined as the lower-dimensional representation of data. Toledo-Marín et al. (Toledo-Marín and Glazier, 2023) stated that a fundamental architectural aspect of GenAI models is that "they rely on the idea that data can be represented in terms of latent variables and these variables are not correlated". The hidden features that the GenAI model identifies are vital for new data production. In Fig. 8, how GenAI helps in Latent Space exploration is depicted. Understanding the toxicology of drugs, chemicals, and compounds accurately is complex. Latent Space exploration can further simplify this (Yang et al., 2022; Into the Latent Space, 2020). In their work, Asperti and Tonelli (Chow et al., 2022) analyzed Vanilla VAE, Vanilla GAN, SVAE, and StyleGAN for latent space exploration.

There are drugs designed to aim at more than one target, known as drug polypharmacology. Latent space exploration assists in identifying the unknown targets of drug polypharmacology, which may lead to harmful effects on health. There are some studies now that are using GenAI for latent space exploration in toxicology. Chow et al. (Chow et al., 2022) applied the VAE latent space to predict cell morphology-based drug polypharmacology for this issue. Similar to (Chow et al., 2022), Gao et al. (Gao et al., 2022) used VAE for the latent space to predict the ecotoxicity of HC50 on the environment. It helps improve in vivo and in vitro toxicity analysis, particularly for artificial chemicals. The following aspects of Latent space exploration or Latent Toxicological Representation that led to enhanced understanding are depicted in Fig. 9 and also given below:

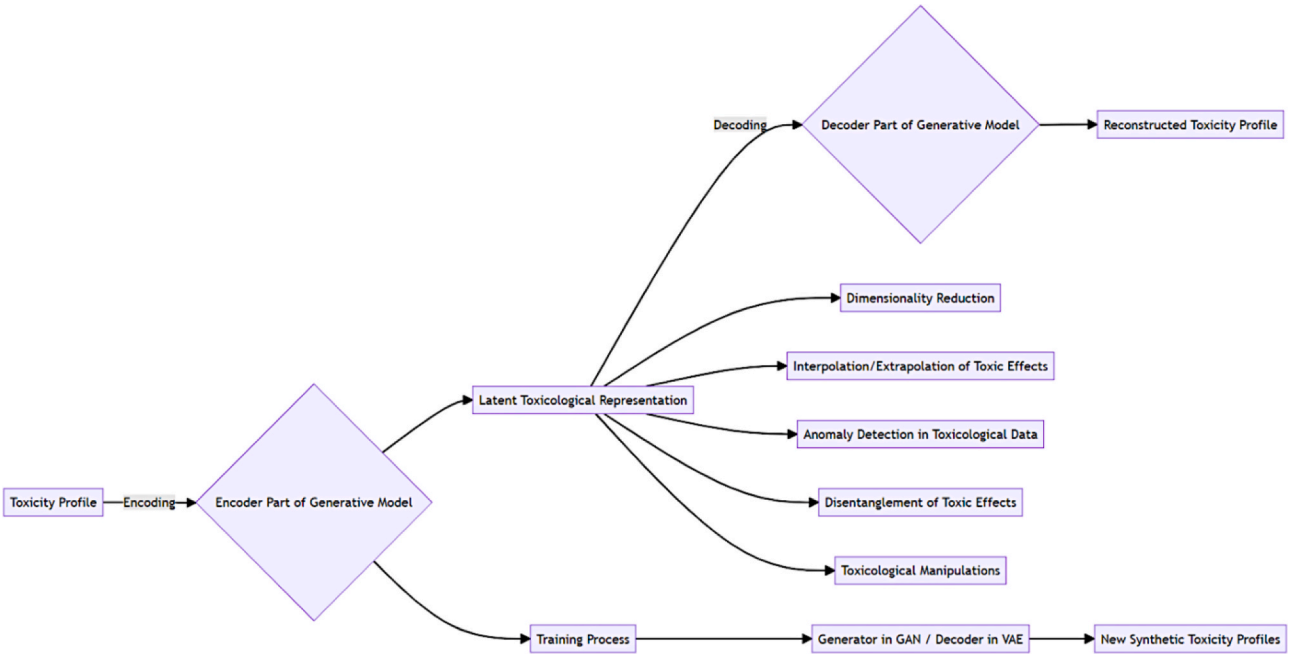

Fig. 9. GenAI process to help in latent space exploration.

- Helpful in dimensionality reduction
- Enhance prediction of toxic effects
- Enhance anomaly identification
- Disentanglement of chemical interactions
- Easier and simplified manipulation

Montero et al. (Montero et al., 2022) and Bandi et al. (Bandi et al., 2023) discuss the architecture and how GenAI processes facilitate latent space exploration in toxicology. However, the authors highlighted several challenges, such as the high dimensionality, completeness, complexity, and diversity of toxicological data, exhaustive computation, and disentangling of latent variables.

2.4.3. *Counterfactual Explanations*

Counterfactual Explanations help explain the prediction of the models by simplifying to understand and explain how the changes in input variables can lead to different predictions (Liu et al., 2019), as depicted in Fig. 10. Counterfactual explanations lead towards making deep learning-inspired AI a white box in nature (Kırboğa et al., 2023), a majorly black box (Prado-Romero et al., 2022). In the field of toxicology, we need white-box AI to answer the following:

- What happened?
- How did it happen?
- Why did it happen?
- How to improve?
- What needed to be altered?
- What are the effects of the changes made?

We can train GenAI models on toxicology data. After training the GenAI models, novel chemical profiles with underlying toxicological properties can be generated (Nemirovsky et al., 2022). By tweeting input variables, favorable toxicological outputs can be obtained by balancing the benefits of drugs and their minimal adverse effects on human health. It further helps in fast drug approval and disapproval and eliminates the unknown territory of how these drugs or chemical compounds behave outside in-house or sample testing (Liu et al., 2019; Numeroso and Bacciu, 2021). GenAI is a perfect fit for Counterfactual explanations in toxicology due to its ability to create feasible or realistic examples. For example, if GenAI predicts that a specific newly invented

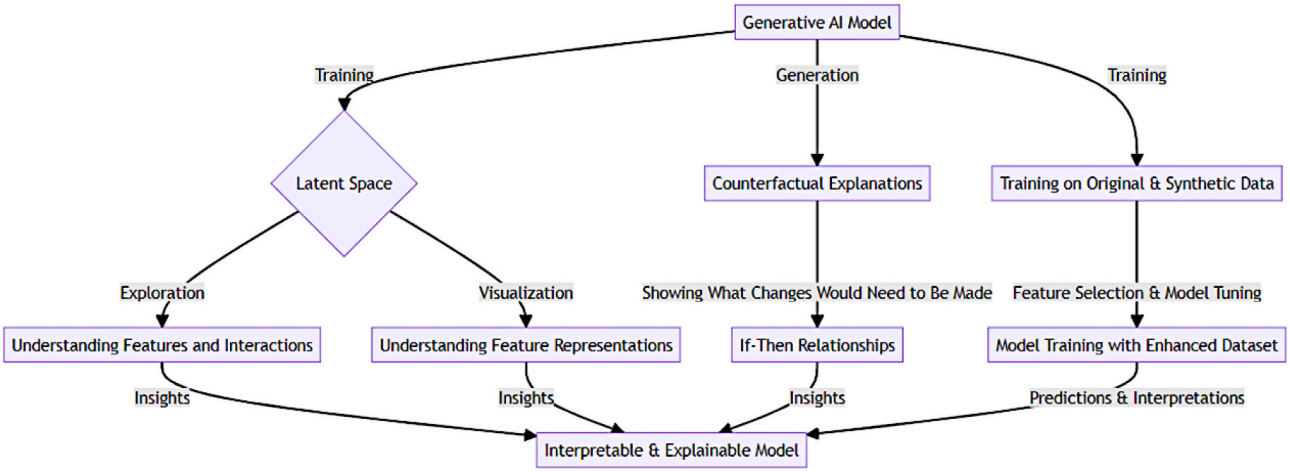

Fig. 10. GenAI process to enhance interpretation and explainability.

chemical compound is nontoxic. However, the counterfactual explanation highlights that the small changes in the chemical will result in a toxic prediction. It could help the pharmaceutical industry avoid drug-to-drug reactions and maintain patient safety. It is critical because it helps to understand the outcomes of the changes. Further interpretable and actionable counterfactuals are produced by GenAI by navigating What-If rules.

2.4.4. Interpretability and Explainability

Interpretability and Explainability terms in AI are often misunderstood as synonyms. However, they are pretty different. Interpretability of an AI model means the extent to which a human can understand why a particular decision has taken place. A reasonable interpretation occurs when decisions are simple and easy to understand. The explainability of the AI model is the extent to which humans can understand the model's decision (Dosilovic et al., 2018; Linardatos et al., 2020). For example, there were two classes: toxic and non-toxic. Chemical' A' is predicted as harmful because the prediction probability of the toxic class is 0.90, and the non-toxic class is 0.10. Interpretation is that the AI model predicts the chemical as toxic because of a higher probability. Explainability is how this AI model reaches this decision of (0.90, 0.10) probabilities.

In recent years, much attention has been given to the interpretability and explainability of AI in life sciences, particularly toxicology, due to its extraordinary ability to simplify, deduce, and reason, which further helps in decision-making and understanding decisions. In a recent review paper, Vo et al. (Vo et al., 2022) analyzed how drug-to-drug interactions can be toxic, which can have adverse effects on health and be life-threatening, and how explainable AI simplifies our atomic-level understanding of these interactions. Several works on the above issues, such as an explainable AI method to predict chemical toxicity in the respiratory system (Jaganathan et al., 2022), TIRESIA for explainable toxicity prediction (Togo et al., 2023), and explainable AI for drug discovery (Jiménez-Luna et al., 2020). However, challenges include the extreme complexity of GenAI models and their black box nature. As depicted in Fig. 10, which is self-explanatory, GenAI fueled interpretability and explainability can be seen as the fusion of latent space exploration, counterfactual explanation, and feature selection, and the same is discussed individually in the above subsections.

Precision medicine, also known as Personalized medicine, is the game-changing approach to treatment where individual patient variability in various aspects of their body, lifestyle, and living environments is considered. Precision medicine is more effective as every human body responds differently to different treatments (Yamamoto et al., 2022; Goetz and Schork, 2018). However, despite having the ability to provide better treatment, Precision medicine is complex. Due to this, it is a costly and time-consuming effort to develop these personalized treatment approaches, as Goetz et al. (Goetz and Schork, 2018) stated, as more resources are needed to reach a stage to provide treatments individually. Some of the significant components of Precision medicine are genomics, pharmacogenomics, molecular profiling, data integration, tailored treatments, cancer treatment, disease prevention, and ethical considerations. Artificial Intelligence has already made inroads in the area of Precision medicine. Johnson et al. (Johnson et al., 2021) critically dis-cussed how Precision medicines can leverage AI to improve healthcare, enhancing clinician decisions. In contrast, Subramanian et al. (Subramanian et al., 2020) the importance of AI applications, especially in treating chronic diseases, as most are more related to individual triggers and responses.

Personalized medicines and treatments are showing significant promising effects in treating cancers (Tran et al., 2021). Xu et al. (Xu et al., 2023) introduced GANs capable of designing high-resolution prostate cancer magnetic resonance images on individual levels. This helps to understand the disease and its progression better. On the other hand, Gutta et al. (Guttà et al., 2023) used GANs with the fusion of gradient penalty and an embedded auxiliary classifier, which can identify low and high-risk patients. Measuring the effectiveness of medicines and treatment is a crucial aspect that can vary from individual to individual. To address this, Yoon et al. (Yoon et al., 2018) proposed GANI, which is the fusion of GANs and the computation of counterfactual information for estimating precision treatment effects, which is considered a difficult task. GANITE can be used for binary treatment only, which is a significant limitation. Ge et al. (Ge et al., 2020) modified the GANs proposed in (Yoon et al., 2018) to overcome this limitation, which can deal with binary and continuous treatments. Several fascinating works exist, such as Kuo et al., where they used self-attention GANs with data generation to measure individual sleep quality. Nowadays, GANs are used to select precision biomarkers, extending GAN usage in precision medicine. Several works exist, such as (Nair et al., 2023; Ai et al., 2023), for groups and community-based biomarker selection for better and more effective healthcare. With recent advancements in GenAI, the paradigm can revolutionize precision medicines (Rosen et al., 2023). However, it is essential to be cautious and not overestimate GenAI as a standalone solution that can deliver final results. The classic or traditional drug development processes (Kandi and Vadakedath, 2023; Restrepo et al., 2023; Boverhof et al., 2011; Gianni and Farrow, 2020; Ma et al., 2021; Palano et al., 2021) extensively help in comprehensive toxicological evaluations, still required to ensure drug safety. A balanced perspective of classic versus GenAI based precision drug development is stated in Table 1.

2.4.5. GenAI vs. Non-GenAI in Understanding Toxicity

The field of toxicology heavily depends on non-GenAI (statistical modeling, conventional machine learning, etc.). It has proved very efficient in understanding various toxicological mechanisms that are further used by multiple regulatory bodies. GenAI excels in data generation, which leads to better understanding of toxicological aspects as more data and diverse data make models learn better. Non-GenAI, such as Principal Component Analysis (PCA) and Random Forest, often used to compute important features and lead to feature selection, are efficacious. However, these methods find it hard to process datasets with complex relationships and other datasets with non-linear dependencies among the features (Pudjihartono et al., 2022). Meanwhile, GenAI, as highlighted in Section 2.4.1, can identify and generate critical biomarkers, facilitating a deeper understanding of toxicological mechanisms. Understanding complex interactions and the importance of computing features can be better than conventional methods such as QSAR, Random Forest, etc.(Ying et al., 2024). This is because Non-GenAI searches in original data space whereas GenAI explores latent spaces (Into the Latent Space, 2020; Schmitt et al., 2024), which better places it in finding the most relevant ones for toxicity predictions.

Non-GenAI methods provide feature importance scores rather than being unable to explain relationships between variables. However, GenAI can generate counterfactual explanations, which is a way to understand how the AI models reach a particular decision for the given input instance, as defined by Ma et al. (Ma, 2022). Additionally, it can simulate a feature's impactn predictions when its values are changed (Mertes et al., 2022). GenAI are black box-based methods. However, Wachter et al. (Wachter et al., 2017) showed that counterfactual explanations are possible without solving black box challenges. The significant characteristics of counterfactual explanations are actionable insights, transparency, causal reasoning, and feasibility that directly improve explainability. Further, non-GenAI methods struggle with multimodal data. GenAI architectures like Transformers, Diffusion models, GANs, and VAEs are flexible as they produce shared latent spaces where a common representation is formed using mapping from different modalities. GenAI is better at fusing multimodal data sources, which are complex and critical in toxicology (Lu et al., 2024; Chen et al., 2024). Non-GenAI is fundamentally more transparent and more straightforward to validate. However, GenAI methods score high on augmenting reasoning and have the power of descriptively explaining like humans but are black box, which increases complexity and needs billions of parameters, which increases computational cost (Bieniek

Table 1
Classical drug development vs. GenAI-based drug development.

Aspect of Drug Development	Classical Drug Development (Examples)	GenAI-based Precision Drugs (Examples)	Comparative Perspective
Target Identification	Genomic studies and high-throughput screening.	AI algorithms analyze complex datasets.	Both methods contribute to identifying targets. The classical methods provide foundational knowledge, whereas AI helps novel insights.
Toxicology Profiling	Animal testing and In vitro assays.	In silico modeling and predictive analytics.	Classical methods offer robust safety analysis. AI assists in early-stage predictive insights. Integration of both can enhance overall profiling.
Development Cycle	Synthesis and iterative testing of compounds.	Rapid in silico screening and optimization of molecular structures.	Classical methods ensure careful detailing, whereas AI accelerates specific tasks. However, full-cycle efficiency is ongoing.
Simulation of Medical State	Animal models, Clinical trials, Organ-on-a-chip technology.	Advanced computer simulations of biological systems, digital twins	Empirical methods are critical for real-world data; AI simulations offer promising supplementary insights.
Treatment Customization	Biomarker-driven drug development, Pharmacogenomics.	AI-driven data analysis for personalized drug profiles and precision medicine algorithms.	There is a rising trend of personalized approaches in both, with AI providing sophisticated analytical tools to complement classical methods.
Clinical Trial Optimization	Adaptive trial designs, Patient stratification strategies.	AI for patient selection and predictive analytics for trial outcomes.	AI tools can augment the optimization of trials. However, we still need to replace the comprehensive approach of classical trials, which are highly reliable.
Clinical Trials	Phased clinical trials and long-term follow-ups.	AI-based design for trial efficiency, Data-driven monitoring systems.	Classical trials provide robust safety data; AI can improve efficiency. However, they cannot be an alternative to extensive empirical testing.
Cost	Clinical trials and research and development are costly.	AI technology development and integration with various drug development processes is expensive.	Both methods are costly, with AI offering potential efficiencies and classical methods justifying costs through thorough processes.
Sustainability	Green chemistry in drug synthesis, waste management strategies.	Reduced need for physical resources in early stages, Energy-efficient AI models.	Sustainability challenges exist, and both are adapting to more sustainable practices.

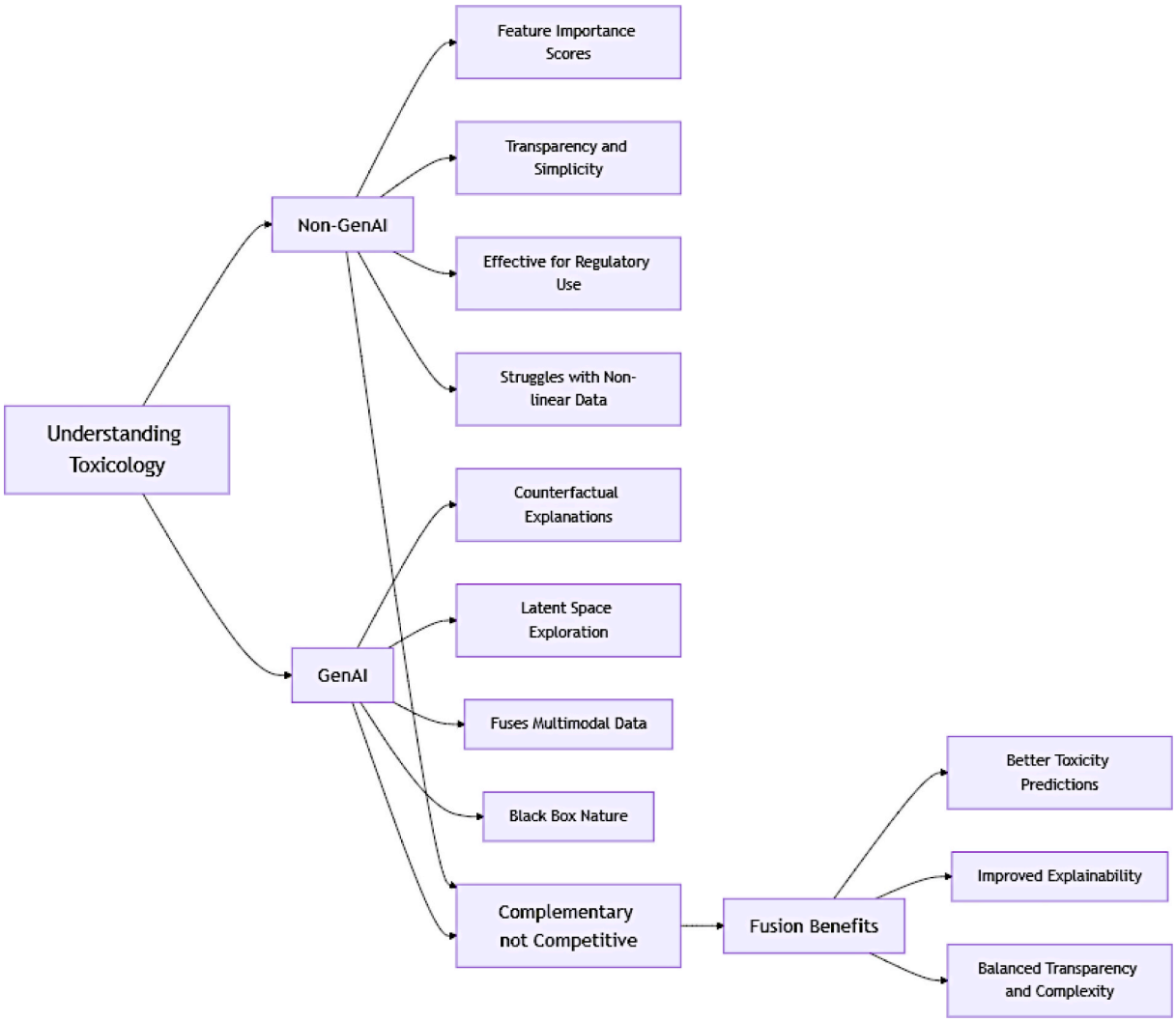

Fig. 11. Comparison of GenAI and Non-GenAI paradigms in understanding toxicology highlighting the unique strengths and challenges.

et al., 2024). As the concluding remarks for the above-reviewed literature in this section and as depicted in Fig. 11, a fusion of both paradigms can be highly beneficial.

2.5. Environmental Toxicology

Environmental toxicology is a sub-branch that analyzes the ill effects of chemicals, gases, and microorganisms on the environment and its organisms, including humans, flora, and fauna. Our environment is a critical element, and even minor toxicity can adversely affect the possibility of human survival on this planet. Studying and forming an optimal understanding of environmental toxicology is too complex due to our need for knowledge of various factors affecting it. Technology, particularly AI, can significantly improve and simplify our understanding of environmental toxicology, which would further help in decision-making to preserve the planet and its species (Miller et al., 2018). The GenAI can help revolutionize our decision-making related to environmental toxicology due to its ability to process multimodal data. Fig. 12, self-explanatory, explains how ecological toxicants affect our planet. GenAI can help predict toxin pathways, forecast their impacts, and suggest remedial ways to counter-manage and control them.

Rapid urbanization is one of the reasons for environmental toxicology, which affects air, water, land, and, ultimately, living organisms, as depicted in Fig. 12. In one such work, Conditional GANs are introduced by Toutouh et al. (Toutouh et al., 2021), which estimate ambient air pollution and help in decision-making for controlling air pollution and forming policies. Another GAN-based work by Wan et al. (Wan et al., 2022) designed a model to identify contamination occurrences in water or water bodies. The proposed GAN model effectively handles a variety of contamination incidents. Soil contamination is increasing, resulting in the contamination of the entire food chain. AI-based methods are successfully used for soil toxicity prediction (Gao et al., 2021). However, the use of GenAI remains absent. It needs to be exploited as it can generate and augment data, improve feature engineering, and help understand complex interactions using representation learning, simulations, etc.

2.5.1. GenAI vs. Non-GenAI in Environmental Toxicology

Environmental toxicology has historically used non-genAI, including supervised, unsupervised, and reinforcement learning techniques for toxicological tasks. Non-GenAI models like Support Vector Machines, Decision Trees, Gradient Boosting Machines (GBM), Random Forest, and Artificial Neural Networks (ANN) have frequently been used in air quality forecasting, water pollution monitoring, and soil contamination assessment (Cui et al., 2023; Wu et al., 2022). These models are effective. However, they need well-structured datasets for training, which can be an issue in tasks where data is scarce, limiting their predictive accuracy. In contrast, GenAI, specifically Generative Adversarial Networks (GANs), Variational Autoencoders (VAEs), and diffusion models, represent a significant evolution in environmental toxicology research by enabling powerful capabilities in data augmentation, multimodal data integration, and predictive analytics (Grekov et al., 2023). GANs, for example, can generate realistic synthetic datasets, addressing the common issue of data scarcity or imbalanced training data in environmental toxicology. Wu et al. discussed in their paper how GenAI can bring innovative and sustainable solutions to provide clean water and electricity. One such work by Wan et al. (Gao et al., 2021) in which they utilized GAN-based methods to simulate contamination events, thereby significantly enhancing model robustness and facilitating proactive water contamination management.

However, GenAI adds new threats to climate change and global warming, which is not true with Non-GenAI. The rapid development and deployment of powerful GenAI-based data centers where these mighty AI algorithms are processing terabytes of data have serious environmental effects as they will increase electricity demand, means more carbon dioxide emissions, and increased water consumption due to cooling systems for data centers means water wastage as stated by Zewe (Zewe, 2025). These algorithms need dramatic architectural changes that decrease their training time and computational resources to make GenAI environment-friendly which will result in less power and water requirements (Zewe, 2025). Today, GenAI is not everybody's tool, but if we want it to be used on a large scale, there is a serious need to make it environmentally friendly, which is not the case now.

2.6. Anomaly Detection

Anomaly Detection in toxicology datasets is crucial, as minor mistakes or assumptions in identifying anomalies can lead to severe implications for human life and the environment. Machine learning and deep learning have long been used for the above-stated purpose (Naylor et al., 1980; Grekov et al., 2023). In the context of toxicology, anomaly detection is critical, and we can use it for:

- Identify anomalies in datasets.
- Predict rare adverse drug reactions.
- Monitor environmental toxins.

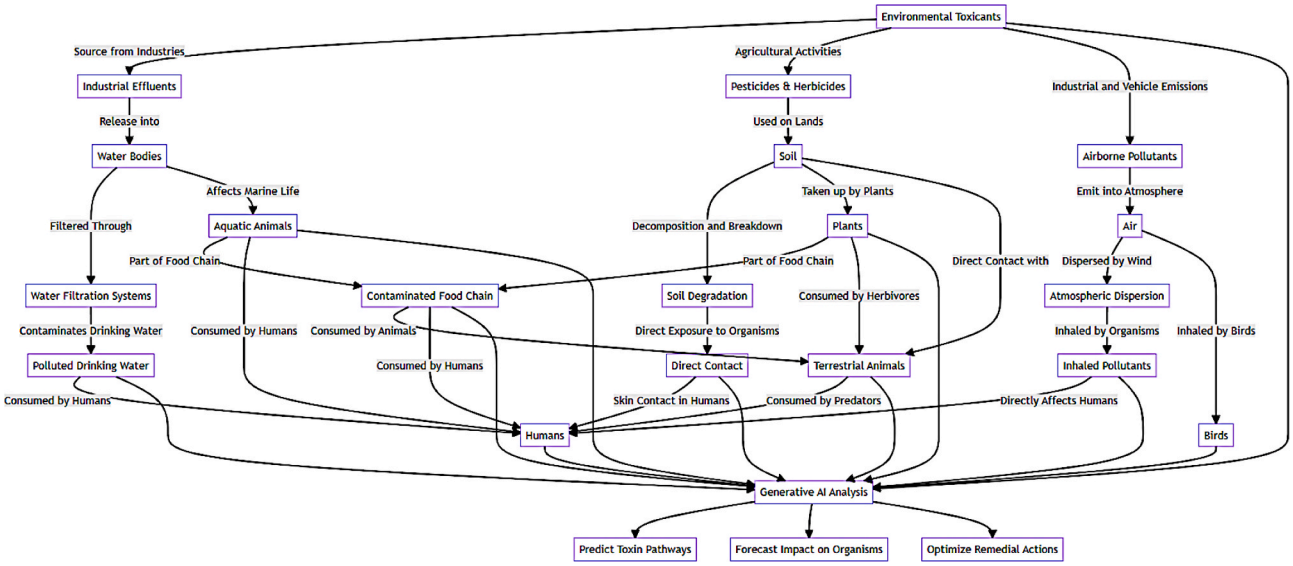

Fig. 12. Effects of environmental toxicants and the role of GenAI in analyzing.

- Predict the toxicity of chemicals.

GenAI methods are better placed when compared to traditional machine learning methods as they are more accurate and can understand non-linearity better. They can produce data instances when limited data is available, particularly in toxicology, when actual data is scarce. Also, having real toxicological data can be a time-consuming and expensive process as it is complex and needs the involvement of various stakeholders (Di Mattia et al., 2019; Xia et al., 2022). Considerable attention is given to multiple domain anomaly detection methods based on GenAI. Geiger et al. (Geiger et al., 2020) and Hoh et al. (Hoh et al., 2022) used GenAI to detect time series data anomalies.

In contrast, Luo et al. (Luo et al., 2022) fused GANs with Convolutional autoencoders for the same purpose. Notably, anomalies must be identified in healthcare and medical problems to understand the adverse effects of drugs, chemical reactions, disease patterns, and treatment outcomes reliably and accurately. Unsupervised GANs are getting popular for identifying underlying false patterns in data. Park et al. (Park et al., 2023) introduced an anomaly detection method using supervised GANs for Unsupervised in one such work. Similarly, Han et al. (Han et al., 2021) proposed MRI images for medical anomaly detection (MADGAN), which used multi-sequences for slice reconstruction for Alzheimer patients. Some other realistic cases where GenAI can be used in toxicology for anomaly detection are vaccine and drug trials, where data is complex. Further, it will speed up development and cut costs. In Fig. 13, a generalized anomaly detection process is depicted for drug trial data, which shows how the process works on a high level. However, some challenges exist, such as toxicology experts needing more expertise to handle and train the GenAI method, which is complex and tricky for the above-stated problems. Therefore, there is a need to develop an expert pool.

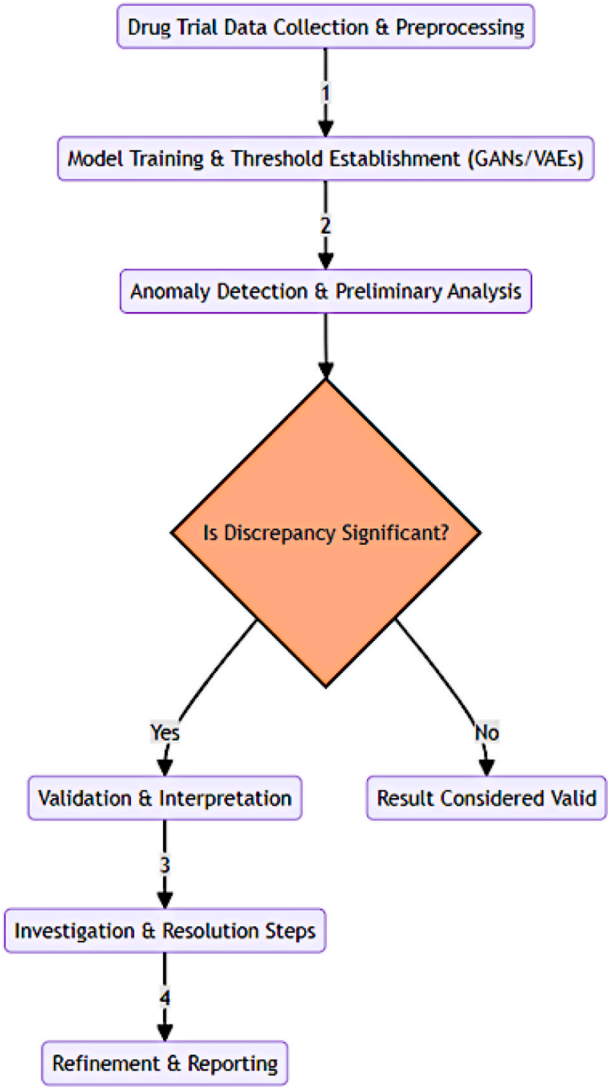

Fig. 13. A generalized anomalies detection in drug trials steps using GenAI.

2.6.1. *GenAI vs Non-GenAI in Anomaly Detection*

GenAI-based methods such as VAEs, GANs, Transformers, and Diffusion can identify outliers with complex deviations that are hard to detect (Gupta et al., 2024). This is powered by how GenAI generates diverse data and processes data using latent spaces (Bewersdorff et al., 2025). GenAI can identify complex biological patterns, apply unsupervised learning without label data, and recognize extreme values that do not belong to different clusters. Additionally, GenAI is powerful in fusing multimodal data (scans, genomic, proteomic, metabolomic data, etc.) (Bewersdorff et al., 2025), which is a typical case in toxicology. This also boosts its ability to identify outliers as it has a multi-perspective understanding of the same context. However, as discussed in the previous sections, computational cost, unreliable models, and hard to explain. Non-GenAI methods are simple and more interpretable as they are primarily white-box approaches, lower computational costs, and are pretty efficient with tabular data. One-Class SVMs (Manevitz et al., 2001) and Isolation Forest (Liu et al., 2008) are examples used to identify outliers, particularly for tabular datasets in toxicology. However, they struggle as the number of features increases and with multimodal toxicological data (Rahate et al., 2022; Wu et al., 2024; Krones et al., 2025). Both Non-GenAI and GenAI have advantages for outlier detection in toxicology. The choice between them or their fusion depends on the problem requirements and mainly depends on data and computational resources. Fig. 14 depicts and generalizes how the GenAI architecture detects outliers or anomalies in the data. Additional Fig. 15 illustrates the roles of latent space in detecting outliers in GenAI.

Latent space is the core of the power of GenAI-based outlier detection, and it is used in conjunction with feature extraction and a reconstruction mechanism. Latent Space is vital in encoding data distribution. New data instances are examined for outliers by computing their distance from normal clusters. Mahalanobis Distance or Kernel Density Estimation (KDE), or by assessing their likelihood within the latent space distribution, are used for this purpose. If GenAI models are unsuccessful in correctly reconstructing an outlier, it means an anomaly in the data, as depicted in Fig. 15.

2.7. *Information Dissemination, Education, and Training*

The Conversational-AI paradigm is where AI mimics conversations in the same manner humans do, or it can be defined as simulating human-like conversations. Generative Pre-trained Transformers (GPT) and Bidirectional Encoder Representations from Transformers (BERT) are standard conversational AI models. Chatbots, virtual customer assistants, and interactive voice response systems are some applications of Conversational-AI (Lin et al., 2023). However, it can have far-reaching effects on our societies. Conversational-AI has no or minimal usage in the toxicology domain, but it holds numerous benefits. However, Conversational AI will have no direct output regarding drugs, vaccines, or treatment. However, it can help in information dissemination, educating and training (IDET) various stakeholders, patient support, research assistance, enhanced emergency response, formulation of better public health policy, and assisting in clinical decision-making processes in toxicology, as depicted in Fig. 16.

In one such work, Abdel-Messih, and Boulos (Abdel-Messih and Kamel Boulos, 2023) analyzed how ChatGPT in clinical toxicology for organophosphate poisoning can answer all critical queries precisely, which helps the poisoned individuals and even healthcare experts to manage the case effectively. Similarly, Hsu et al. (Hsu et al., 2017)

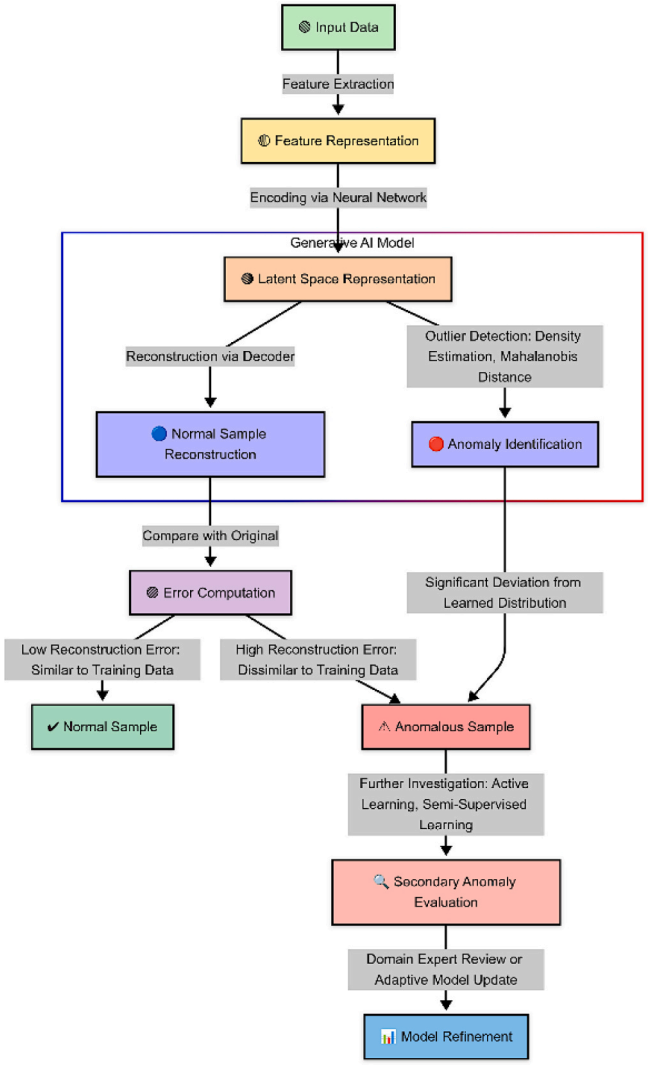

Fig. 14. Generalized GenAI Architecture for Anomaly.

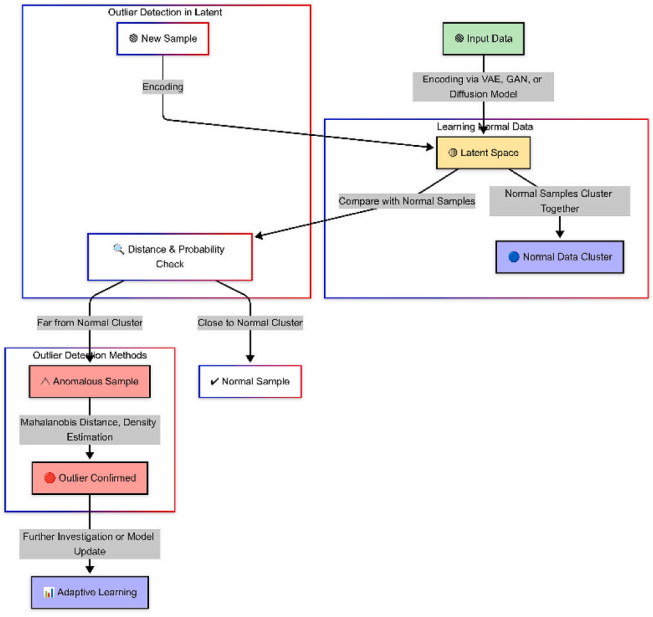

Fig. 15. Role of latent space in detection outliers in GenAI.

proposed AllergyBot, which informs individuals about food allergies when dining in a restaurant. Both (Abdel-Messih and Kamel Boulos, 2023; Hsu et al., 2017) help to educate and inform various stakeholders on the subject matter. It prevents the physical need for an expert and can be life-saving by reducing response time and being cost-effective. Further, these chatbots cannot just interact but learn from previous experiences and form a solid basis to address further research and enhance public healthcare policies.

Chatbots have been successfully used during the Covid-19 pandemic. Particularly in rural and remote areas where doctors are not readily available, chatbots educate people on how to avoid getting infected and guide them in managing COVID-19 patients. However, it is still not used on a large scale due to the non-availability of internet and interaction devices (Almalki and Azeez, 2020; Battineni et al., 2020; Stieglitz et al., 2022). Further, these Chatbots can share experiences and outcomes of specific expected treatments, which is a convergence to GenAI. Conversational-AI can speed up emergency response during potential poisonings or chemical exposures. Without a medical expert, it can assist individuals and inexperienced medical professionals in taking necessary steps and handling medical emergencies. Conversational AI applications are growing and diverse now. For example, in (Kocielnik et al., 2021), a chatbot can assist medical professionals in better comprehending the social requirements, such as food, accommodation, and non-medical essentials, of arriving emergency room patients. Another important thing needed, especially in events such as COVID-19, is information dissemination, which spreads information regarding a specific event or emergency that concerns the masses. For example, governments worldwide have done advertisement campaigns regarding washing hands, using masks, avoiding crowds during Covid-19, and promoting the importance of vaccination in digital and print media. The main objectives of information dissemination are to educate, influence, update, and alert. What we have discussed above helps improve goal-focused decision-making, which is complex, particularly in the toxicology domain, where new chemicals, drugs, and treatments are designed and evaluated.

Further, we can inter-act and argue the pros and cons of Conservational AI systems regarding our possible decision (Hsu et al., 2017; Klambauer et al., 2023). It helps to identify any missing points that we haven't considered. It will also result in minimizing the decision error rate by interacting with GenAI systems and vice-versa, allowing the user to scrutinize the output and clear doubts. For example, ChatGPT, an advanced chatbot application, and the Generative Pre-trained Transformer (GPT) algorithms are the technology that powers it for highly sophisticated data analysis, reasoning, and prediction capabilities. We can cross-question ChatGPT output and request reasoning with supportive biological evidence. ChatGPT produces evidence to prove that a particular outcome or prediction is accurate. The whole process will result in more grilled output and its validity. ChatGPT chatbots help reduce uncertainty using decision support and information provision (Ahmed et al., 2023; Roumeliotis and Tselikas, 2023). Therefore, the chances of error decreased considerably. Conversational-AI gives GenAI more relevance when fused and applied to solve a toxicological problem. Despite the advantages discussed above, some critical challenges remain. Based on the above literature, we depicted in Fig. 16 the Conversational-AI landscape for the toxicology domain, which consists of its applications, various stakeholders, key aspects, advantages, and disadvantages.

2.7.1. GenAI Added-Value over Non-GenAI in IDET

GenAI is not just a good tool but outperforms Non-GenAI in information dissemination, education, and training (IDET) tasks due to its architectural advancements, advanced NLP capabilities, context modeling, reasoning capabilities, informed decision-making, and real-time adaptability and interactivity capabilities (Yan et al., 2024; Kumar et al., 2025), and the same is depicted in Fig. 17. From architectural advancements, transformers-based GenAI models (GPT, BERT,

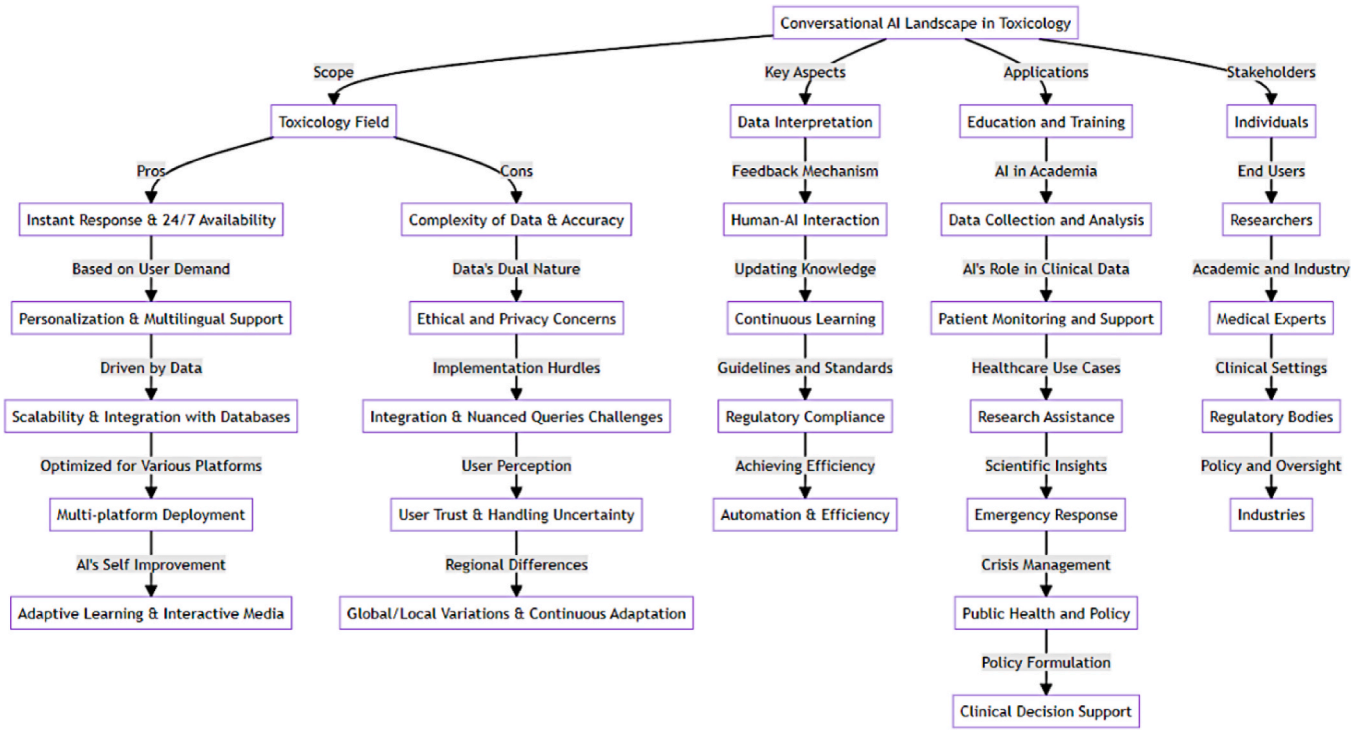

Fig. 16. Conversational-AI landscape in toxicology.

T5, etc.) have two powerhouse features: attention mechanisms and positional encoding (Islam et al., 2024). Attention mechanisms help understand complex content sequences and produce coherent and contextually relevant educational and training content. Attention mechanisms also power summarization capabilities, where the most critical information is found in the high content volume (Vaswani, n.d.). Whereas Non-GenAI generally doesn't have the leverage of attention mechanisms.

Non-GenAI models like Recurrent Neural Networks (RNNs) and Long Short-Term Memory (LSTMs) do sequential processing, i.e., one token at a time, making them slow and computationally costly for long toxicology materials. Further, models like RNNs suffer from vanishing gradient issues as retaining information over long toxicology documents is challenging. Meanwhile, GenAI models such as transformers (Yan et al., 2024) leverage attention mechanisms and positional encoding to capture long-range dependencies efficiently. Non-GenAI models like CNN are good with images. Still, they are architecturally weaker in understanding sequential data (Alzubaidi et al., 2021), leading to failure in understanding sentence structure, a crucial aspect of information dissemination and educational content generation in toxicology.

Additionally, other conventional machine learning algorithms, like SVM, Decision Tree, etc., cannot understand "cause-effect relation," which is a must to have the ability for efficient information dissemination, interactive education, and training. GenAI models, like diffusion models, can create educational images for toxicology. For example, explaining molecular interactions visually. Visual content is critical in information dissemination, education, and training objectives. GenAI models and tools (Mid Journey, Open AI's Sora, etc.) are now widely available which have extraordinary capabilities to understand images, explain visual figures, diagrams, scans, and make informed decisions with strong reasoning, which lacks in non-GenAI completely. In summary, and as depicted in Fig. 17, Non-GenAI does not match GenAI methods, particularly in IDET tasks.

3. MolGAN and Variants Case Study

Identifying toxic and non-toxic compounds is a significant challenge to ensure drug development and chemical safety. Many drug candidates are effective in curing a medical condition; however, around 30 % (Sun, 2022) are rejected due to their toxic nature in clinical trials. Due to this fact, early-stage detection tools are needed for toxicity detection and to mitigate toxicity risk, as later-stage vivo tests are costly. To handle this challenge, De Cao and Kipf introduced GenAI-based Molecular Generative Adversarial Networks (MolGAN) (De Cao and Kipf, 2018), which create novel graphical molecular structures. MolGAN can be trained to develop new chemical structures that are bioactive and safe. This gives strength to the process of drug selection in the early stages. MolGAN can efficiently search chemical space for structures that have specific toxicology profiles. The GenAI capabilities of MolGAN help intelligently design non-toxic molecules. Further, it saves time and money as it minimizes the chances of late-stage drug failures as a result of toxicity.

3.1.2. MolGen Methodology

MolGAN methodology, as depicted in Fig. 18, starts by preparing suitable molecular and configuring the MolGAN parameters for graph-based molecule generation. The next step is to train the model so it has a high chance of producing low-toxicity outputs. Lastly, the generated molecules are analyzed for toxicity. MolGen uses a generator and a discriminator to create molecular graphs and distinguish real from generated molecules. A reward network is used to evaluate molecule properties. MolGAN optimizes a GAN and reinforcement learning objective using a Deep Deterministic Policy Gradient (DDPG). Fig. 18 is self-explanatory and explains in detail how MolGAN functions.

During training, latent vectors generate candidate molecules, and the discriminator improves chemical realism. In contrast, Reinforcement learning reduces non-toxicity, which balances GAN loss and reward. Penalties are put in place to reduce chemically implausible outputs. Strikingly, MolGAN can produce nearly 100 % valid molecule yields. For performance evaluation, the initial step is to measure the validity and

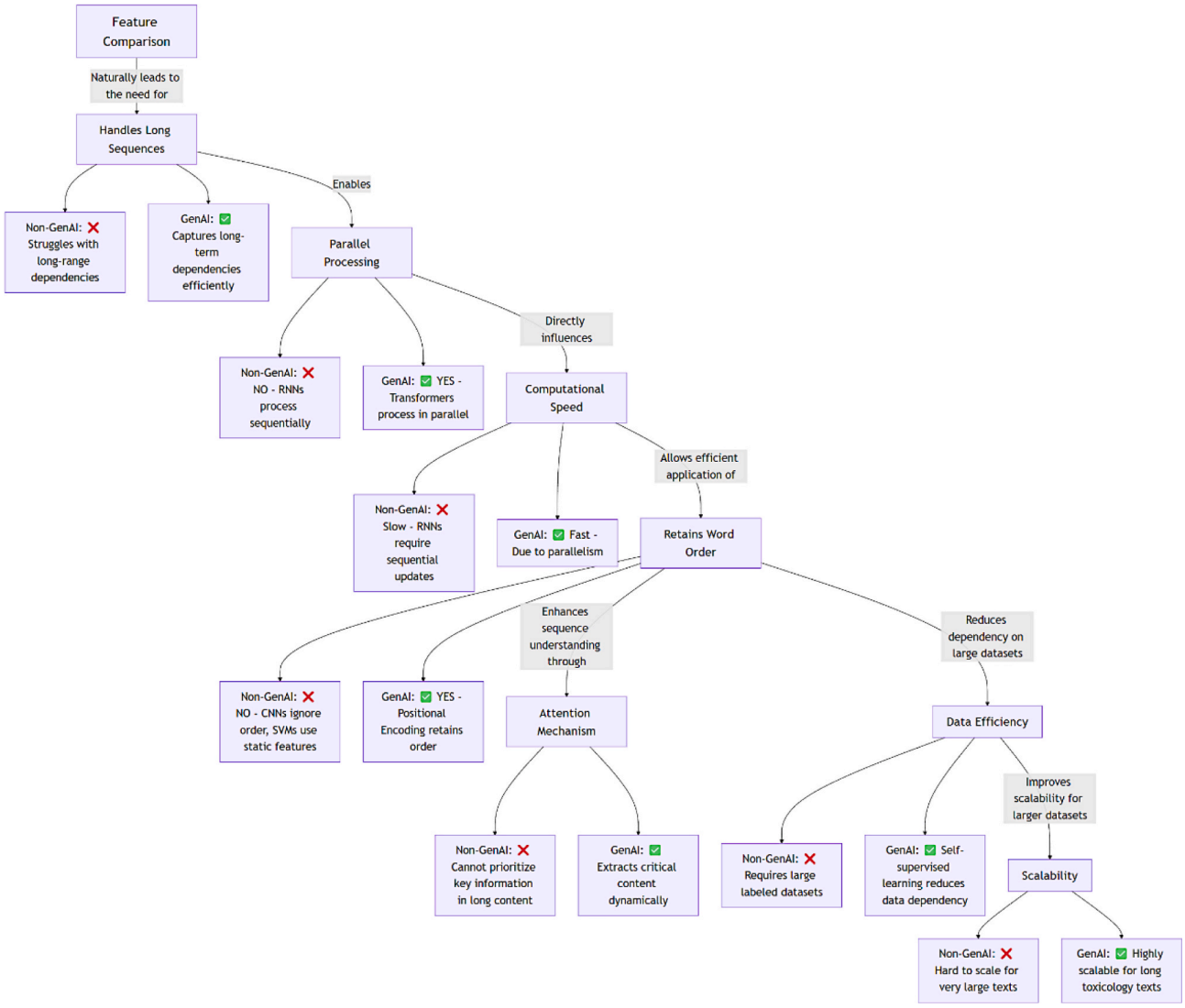

Fig. 17. Generative AI (GenAI) dominates information dissemination, education, and training (IDET) tasks.

uniqueness of the generated molecules. After that, toxicophores are used to measure the toxicity of generated molecules. Additionally, drug-likeness benchmark metrics are used, which include a quantitative estimate of drug-likeness (QED), lipophilicity (LogP), molecular weight, and synthetic accessibility (SA).

3.1.3. *Implications and Applications*

MolGAN-like methods successfully produce low-toxicity molecules, which help reduce efforts. Non-GenAI methods make the molecule and then test its safety. Meanwhile, MolGAN, like GenAI, considers safety first and tries to design non-toxic or low-toxic molecules. The whole process is time-efficient and cost-effective. MolGAN not only takes care of safety but is very helpful in discovering new de-risked molecules which are previously unknown, which have considerable implications for drug pipelines, where the downstream success rate is higher. It also means avoiding or reducing animal testing. From a multi-disciplinary and technological perspective, an essential implication of MolGAN is facilitating collaboration between toxicologists, chemists, and AI experts.

3.1.4. *Applications*

GenAI-based MolGAN has various critical applications in toxicology today. First is the early-stage lead discovery process, which is created by tuning and applying MolGAN, and then virtual libraries of candidate molecules are made that can satisfy essential safety criteria in silico, the outcome of which is high-potential, low-risk leads to advance into experimental testing. The second practical application of MolGAN is in lead optimization. MolGAN can be used to design safer chemicals from outside the drug domain. Additionally, it can help in predictive toxicology by creating hypothetical compounds to test the performance of predictive models, which will significantly assist researchers. A model can be tested by generating challenging borderline cases to assure regulatory agencies of performance. An interesting development where a quantum-enhanced MolGAN is proposed is where MolGAN architecture is modified using quantum circuits that perform better than GAN in generating molecules with specific safety profiles (Insilico Medicine, 2023; John Potter, 2023). These advancements show us that the role in AI-driven toxicology is on the rise due to its overall efficiency.

3.1.5. *Benefits and Limitations*

MolGAN has various benefits that can help enhance drug safety and

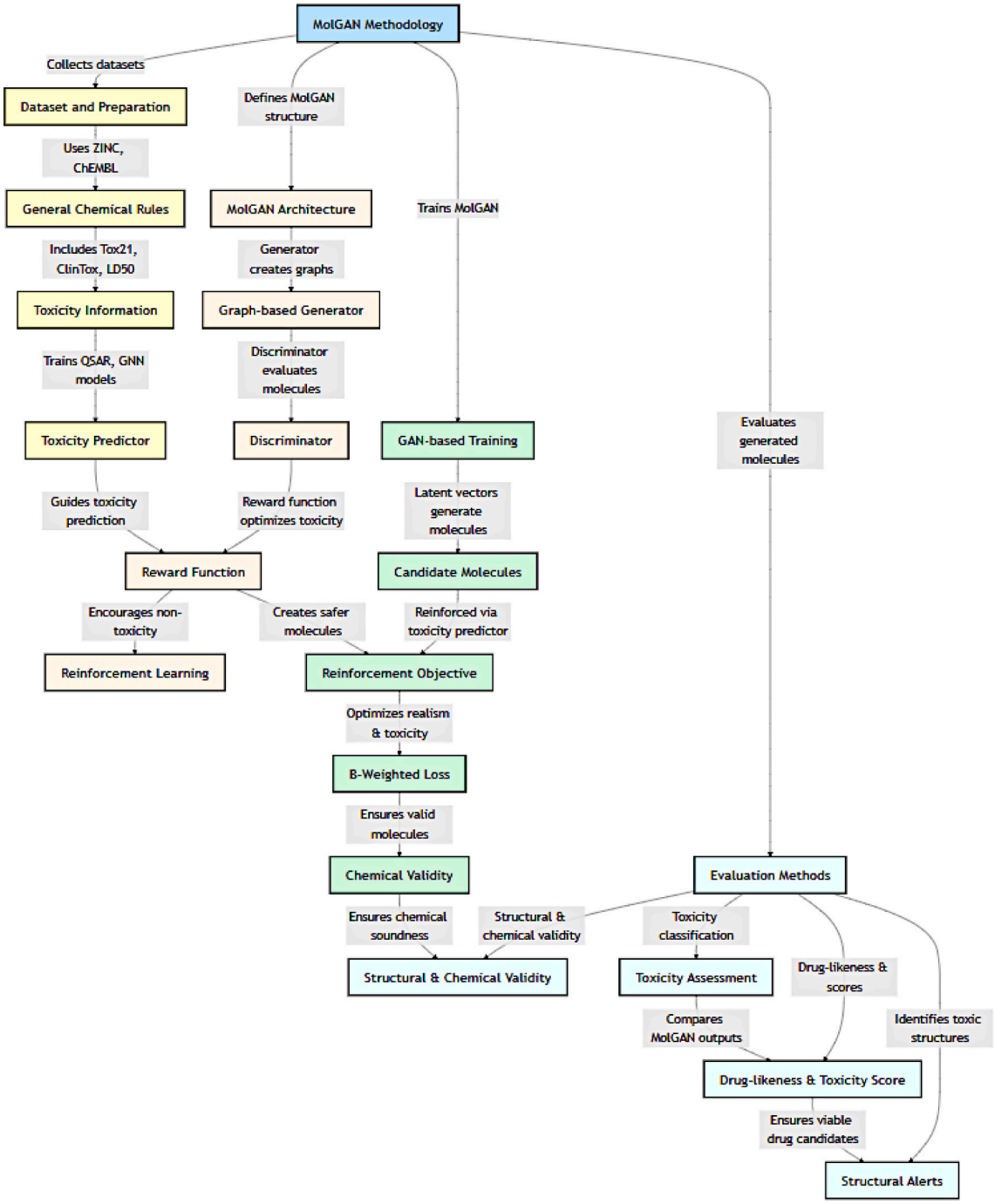

Fig. 18. Methodology of MolGAN.

efficiently use time and cost. However, there are some limitations to MolGAN, which are filled by several variants like L-MolGAN. Table 2 discusses precisely the various benefits that MolGAN brings to toxicology. Additional limitations of MolGAN are also discussed in Table 2.

3.1.6. Customized MolGAN Variants

Classical MolGAN performs effectively for small molecules (≤9 heavy atoms) at mentioned in Table 3. However, the significant limitations in scalability in designing larger molecules Table 4. To overcome this limitation and design large molecules, L-MolGAN is proposed by Tsujimoto et la (Aven, 2016) which is based on adding a penalty for disconnected graphs. It results in a connectivity reward during the training of MolGAN, which produces larger molecules of up to 20 atoms. L-MolGAN has better scalability and connectivity. However, it has a more complex traninng process, which may require sufficient tuning knowledge. A comprehensive architectural comparison between MolGAN and L-MolGAN is given from Table 2 to Table 5.

4. Risk Assessment and Management

Risk assessment and risk management are two interconnected and sequential processes in toxicology (Aven, 2016). In risk assessment, risk is analyzed or assessed concerning a chemical, process, or treatment (Younes and Georgiadis, 2020). Individuals and expert groups can evaluate risks. In risk management, decisions of action that would be

Table 2
MolGAN benifits vs limitations.

Aspect	Benefits	Limitations
Molecular Size Limitations	Generates molecules as graphs, ensuring structural validity and correct bonding patterns.	Encounter issues with molecules beyond ~ 9 heavy atoms and beyond ~ 20 heavy atoms.
Generation Approach	One-shot molecule generation improves efficiency in terms of time and cost over atom-by-atom methods.	Mode collapse leads to low diversity, causing the model to generate repetitive structures.
Optimization Performance	Reinforcement Learning (RL) effectively steers molecules toward desired toxicity properties, making it useful for toxicity-aware molecule design.	RL optimization can cause mode collapse due to overfitting.
Scalability	L-MolGAN extends MolGAN's capability, enabling connectivity fixes and allowing molecules up to 20 heavy atoms.	Scaling beyond 20 heavy atoms remains challenging, and 50 heavy-atom drug-sized molecules are still impossible.
Multi-Objective Handling	It can optimize molecular properties toxicity, efficacy, and synthetic accessibility simultaneously, making it flexible for various drug discovery tasks.	Over-optimizing one property (e.g., non-toxicity) may degrade others (e.g., making molecules hard to synthesize or chemically unstable).
Data Efficiency	Learned from structured chemical datasets, avoiding the need for predefined molecular rules.	Performance depends on the quality and diversity of training data; rare toxic chemotypes may be underrepresented, leading to biased results.
Chemical Creativity	Can propose novel molecular scaffolds that may evade known toxicophores, offering potential breakthroughs in drug design.	Lacks interpretability—does not explain why a molecule is predicted as non-toxic, making it harder for chemists to trust the results.
Training Stability	Improving molecular properties over time by adversarial training with RL to refine molecule generation iteratively,	GANs with RL objectives are hard to train, requiring extensive hyperparameter tuning and meticulous reward balancing.
Chemical Validity	Ensure realistic valency and bonding, it produce molecules with nearly 100 % validity in small molecule domains,	It may create chemically valid but impractical molecules.
Toxicity Prediction Dependence	Integrating external toxicity predictors to guide molecule generation improves drug discovery safety.	It is exposed to reward hacking, where the generator finds loopholes in the toxicity model.

Table 3
MolGAN vs L-MolGAN Generator Architecture.

Feature	MolGAN	L-MolGAN
Input	Random latent vector z	Random latent vector z
Output	Molecular graph as adjacency and feature matrices	Molecular graph as adjacency and feature matrices
Graph Representation	Nodes represent atoms, edges represent bonds	Similar, but with explicit connectivity constraints
Graph Construction	Implicit adjacency matrix generation	Reinforced adjacency matrix with a connectivity penalty
Objective	Generate realistic molecules	Generate realistic and fully connected molecules
Reinforcement Learning	Uses Deep Deterministic Policy Gradient (DDPG) for property optimization	Uses DDPG with connectivity-aware rewards
Scalability	Struggles with molecules ≥ 9 heavy atoms	Can generate molecules with up to 20 heavy atoms

Table 4
MolGAN vs L-MolGAN Discriminator Architecture.

Feature	MolGAN	L-MolGAN
Function	Classifies generated vs. real molecules	Classifies molecules, with additional validity constraints
Graph Encoding	Uses Graph Convolutional Networks (GCNs)	Uses Extended GCNs (E-GCNs) for larger graphs
Optimization	Standard GAN loss function	GAN loss + explicit connectivity loss

Table 5
MolGAN vs L-MolGAN Reward Function (Reinforcement Learning).

Feature	MolGAN	L-MolGAN
Reward Function	Optimizes for drug-likeness, QED, and LogP	Optimizes for validity, connectivity, and toxicity constraints
Structural Penalties	None (can generate disconnected graphs)	Penalizes disconnected graphs
Toxicity Control	External toxicity predictors can be integrated	Built-in toxicity optimization via reward tuning

taken to mitigate identified risks are taken (Hertel et al., 2014). Organizations and the government generally have the capacity, resources, and authority to make standards and regulations with strict compliance for risk management. Agencies and organizations, which include but are not limited to The World Health Organization (WHO), United States Food and Drug Administration (FDA), United States Environmental Protection Agency (US-EPA), European Chemicals Agency (ECHA), and European Food Safety Authority (EFSA) are responsible for risk management (Hertel et al., 2014; Persad and Toxicology, 2020). The following subsections will discuss risk assessment, its management, and toxicological and chemical databases.

4.1. Risk Assessment

Risk assessment (RA) is where we study risks associated with particular drugs and chemicals, and it is central in decision-making during risk management. Toxicological RA, generally empirical studies, have shifted toward AI for robust analysis (Lin and Chou, 2022; Hartung, 2023). Applications of GenAI can revolutionize the area of risk assessment in toxicology. However, not much attention has been given to this. Fig. 19, self-explanatory, shows the possible GenAI landscape in RA. There are four stages in RA, as discussed by Míguez (Míguez and Identification, 2024) (1) Hazard Identification, (2) Dose-Response Assessment, (3) Exposure Assessment, and Risk Characterization. Hazard identification is one of the initial steps in risk assessment, where toxicological experts scrutinize the drugs and the chemical compounds. The main goal is to find clues about potential adverse effects. The second step is the dose–response assessment, which quantifies the relationship between dose and toxicity using statistical models (Linden et al., 2016). Further, an Exposure Assessment analysis is performed, where the extent of the population's exposure to toxic agents is analyzed. Location, time of dose, and quantity of dose contribute to Exposure. Finally, risk Categorized is carried out, where knowledge from hazard identification, dose–response assessment, and exposure assessment is integrated. A qualitative or quantitative estimate is calculated to identify overall risk and discuss possible uncertainties (Míguez and Identification, 2024; Linden et al., 2016; Ochoa, 2018).

GenAI use in toxicology remains in its infancy today for the tasks of RA. However, it is getting the attention of the scientific community now. In one such work, Kattamreddy and Chinnam (Kattamreddy and Chinnam, 2025; EPA, 2024) give the prospect of large language models (LLMs) importance in transforming toxicological risk assessment (RA)

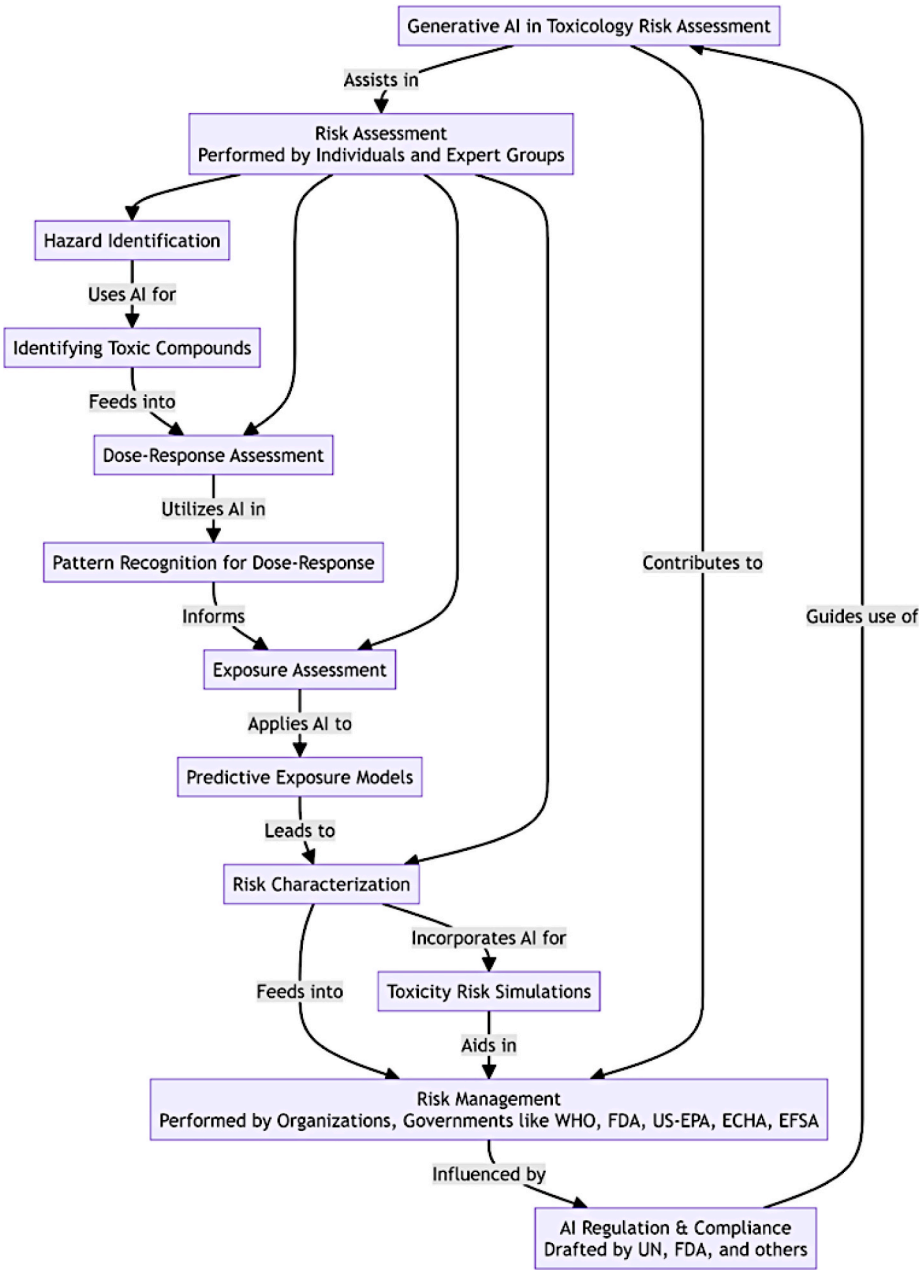

Fig. 19. GenAI landscape in Risk Assessment (RA).

by enhancing precision and adaptability in decision-making. Non-GenAI methods of RA depend on single-stressor models, which limits their ability in RA. However, the GenAI method can give us better contextual awareness of real-world situations because of its ability to do real-life risk simulation (RLRS), multi-stressor models, and dynamic exposure modeling. Further, a pilot project is in progress launched by US EPA (EPA, 2024) for chemical risk assessment using models including Azure OpenAI and Llama3. These models assist in justifying the decisions and enhance reviewer efficiency.

GenAI helps understand chemical structure to identify hazards in the early stages of chemical development. It can also contribute to dynamic risk profiling, where data is updated in real-time, improving hazard assessment models. Also, the ability of GenAI, particularly GANs, assists data generation, which helps in better analysis in cases where data is not available in large quantities, and it helps minimize animal testing (Chen et al., 2023; of Sciences Engineering, 2022). AnimalGAN and Tox-GAN are two GAN-based methods focused on implementing 3R principles and analyzing hazard assessment. AnimalGAN (Chen et al., 2023) ranks the drug's hepatotoxicity, whereas Tox-GAN (Chen et al., 2022) uses toxicogenomics, where the paper explores the chemicals in gene expression. It is an advanced technique for hazard assessment. Wang et al. (Wang et al., 2022) proposed a Risk Categorization framework which moved beyond the traditional toxicological RA. It examines and discusses the use of GANs to improve radiation therapy, considering the safety standards. Still, RA is majorly dependent on traditional statistical and empirical studies. Not much attention has been given to applications of GenAI. However, the fusion of GenAI into toxicology can redefine RA by improving precision in predicting toxicity. GenAI can simulate complex biological interactions, help identify potential hazards, simplify the evaluation process, and refine risk profiles, which signals a transformative phase in toxicological RA.

4.2. Risk Management

Once we finish assessing the risks, we need to take action to minimize the toxic effects of estimated risk on human health and the environment. In risk management, we need to decide how to mitigate risks. WHO, FDA, US-EPA, ECHA, and EFSA focus on chemical safety, leading to health and environmental protection. The organization introduced several toxicological RA and management procedures to monitor chemicals' harmful effects and usage(Hertel et al., 2014; Persad and Toxicology, 2020). Due to the increasing use of AI technologies in toxicology, these organizations are slowly introducing various AI standards and policies that must be followed to minimize and control toxicant effects on humans and the environment. WHO officially published news (WHO, 2021; WHO, 2021) focusing on benefiting from AI in health risk management. However, the WHO has also warned of the potential dangers of AI and has urgently called for policies and frameworks to address this. WHO published a detailed book on being careful about health-associated AI technologies (WHO, 2021). WHO, in this work, stresses that AI can undermine human autonomy as AI will be capable of making decisions independently. It will remove shared decision-making, to which humans can contribute, giving ultimate control to these AI technologies as they are prone to errors and biases. WHO echoes powerful sentiments supporting a cautious approach to AI in human health and risk assessment rather than blind use (WHO, 2021; WHO, 2021; WHO, 2021).

The EPA (EPA, 2023) has an inventory containing AI-related projects per Executive Order 13960. Its objective is to increase the trustworthiness of AI technologies in federal governance. EPA's AI initiative is focused on using AI to improve toxicology and chemical expo-sure analysis. The critical aspects of this EPA initiative are focused on prognostic analysis of chemical exposure routes and developing unified AI modeling approaches for chemical intake. The Integrated Risk Information System (IRIS) (Cavalli et al., 2022) initiative of EPA assists in recognizing and categorizing hazards from environmental chemicals affecting human health. The FDA issued a discussion paper on Software as a Medical Device (SaMD) (FDA, 2019) and requested feedback on AI, which introduces an outline map for a regulatory framework in products and technologies related to human health assessment, diagnostics, and treatment. The focus is assessing and managing risks in SaMD, fused with AI. EFSA, in its report (Cavalli et al., 2022) is set to upgrade and improve its risk assessment processes by powering them with AI by 2027. The focus will be to boost the management processes and chemical-related analysis to improve human and environmental safety. EFSA believes that its capacity to use and analyze diverse and large chemical datasets will be enhanced significantly by using AI. It will eventually assist in in-depth and reliable chemical analysis. The processes will be more transparent and resource-efficient. Further, EFSA (Cagnoni et al., 2023) analyzed the integration of AI for analyzing risk in toxicological chemical datasets. EFSA and external authors in this work focused on chemical safety evaluation by improving document reviewing processes.

Tools like DistillerSR and ASySD are compared, and it is noted that the use of AI resulted in improved chemical risk assessments, with the need for diminished effort and time. The inception of Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) regulations in Europe were introduced in 2006 to protect humans and the environment from the toxic effects of the chemicals. ECHA was established to facilitate the implementation and enforcement of the REACH regulations (Klika, 2021). Later, REACH was also part of The European Green Deal (C. from the Commission, 2019), committed to a toxic-free environment. As per Reuter (Parodi et al., 2023), in their report, countries worldwide race to make policies and regulations to streamline the use of AI in various fields, including human health. The risk assessment procedures focused on leveraging AI benefits and policies are focused on making regulations and standards that are cautious about excessive faith in AI-based technologies. Table 6 summarizes the literature related to multiple risk assessment and management aspects.

Table 6
Cross-sectional synopsis of the Risks Associated with AI in Health and Chemical Hazard Analysis.

Source	Objective	Impact	Relation RA
Chen et al. (Chen et al., 2023)	AI alternative to animal studies	Ethical research advancement	Promotes ethical health RA
Wang et al. (Wang et al., 2022)	GANs in radiotherapy	Cancer care innovation	AI in radiotherapy RA
WHO (WHO, 2021)	AI risks to human rights	Ethical awareness	AI impacts on human rights risk
WHO (WHO, 2021)	AI guidance for healthcare	Global healthcare quality	Guides AI in healthcare risk management
WHO (WHO, 2021)	AI ethics and governance in health	Ethical healthcare guidance	Concentrated on AI ethics in health risk
EPA (EPA, 2023)	AI in environmental management	Showcases governmental AI use	AI in environmental risk management
EFSA, Cavalli et al. (Cavalli et al., 2022)	AI application in food RA	Advances food safety	Enhances food safety AI assessment
FDA (FDA, 2019)	AI application in medical device regulation	Safe medical device innovation	Framework for AI in health risk
Cagnoni et al. (Cagnoni et al., 2023)	AI in vertical use cases	Precise food risk analysis	Applies AI to risk scenarios
Klika (Klika, 2021)	EU chemicals policy enforcement	Influences chemical policy	Directs chemical risk management policy
EC (C. from the Commission, 2019)	The European Green Deal	Environmental policy impact	AI in Environmental Risk Policy
Parodi et al. (Parodi et al., 2023)	Regulation of AI tools	Shapes AI regulation	Addresses AI regulatory aspects in risk
NASEM (E. and M. National Academies of Sciences, 2022)	AI for chemical hazard assessment	Improves hazard assessment accuracy and safer chemical usage.	Guides AI in chemical RA
Thayer et al. (Thayer et al., 2022)	Systematic evidence mapping	Streamlines RA	Improved chemical risk analysis methods
Chen et al. (E. and M. National Academies of Sciences, 2022)	AI in toxicogenomics	Advances ethical toxicological research	AI approach for toxicogenomic risk
QSAR Models (Zhang et al., 2023)	Molecular property predictions	Chemical RA aid	AI enhances QSAR model
BMDS (Chen and Chen, 2014)	Analyze dose & response relation	Precision in RA	AI improves RA precision
RAIS (ORNL, 2023)	Environmental RA toolkit	Environmental analyses	AI models environmental risks
ICE Models (Raimondo and Barron, 2020)	Species Pesticide Sensitivity Modeling	Enhanced ecological RA and management strategies	AI-based ecological risk prediction
EpiSuite™ (EPA, 2023)	Chemical property and fate estimation	Environmental impact prediction	AI simulates environmental impact risks
TEST (EPA, 2023)	Toxicity estimation tool	Rapid toxicity estimation	AI speeds up toxicity management
CTD (Mattingly et al., 2006)	Chemical-disease mechanisms	Chemical-disease understanding	AI uncovers molecular risk factors

4.3. Databases and Tools

Toxicological and chemical databases PubChem (Kim et al., 2016),

TOXNET (NIH, 2023), ChemSpider (Pence and Williams, 2010), ECHA (Musset, n.d.), IRIS (Woodard et al., 2009), TOXLINE (McHale et al., 1986), HSDB (Fonger, 1995), CPDB (Gold et al., 1991), and TOXRIC (Wu et al., 2023) play a critical role in risk assessment as they are the source of periodically updated and systematically arranged stored information that can be used for analysis, regulatory compliance, and research and development. AI has brought about a significant metamorphosis, particularly in how databases are exploited, as stated in Table 7. However, as analyzed, the majority still lacks real-time updates. It is critical, for example, in a pandemic like COVID-19, where we need to develop and approve new drugs and vaccines in a short duration compared to the classical development and licensing cycle. Despite limited data, GenAI can augment data, which will help understand the underlying risk patterns of proposed drugs and vaccines and eventually help improve risk management in a short time. Data anomalies can also be detected (Lee et al., 2023), meaning high-quality data stored in databases. Further, GenAI can potentially improve database management (McKendrick, 2023). From the above literature, we can conclude that well-maintained toxicological databases with high-quality data will benefit the risk analysis, and ultimately, we can achieve optimal risk management.

4.4. GenAI Model's Validation

Model validation plays a critical role in the broader risk assessment and management framework in toxicology. A successful risk assessment largely depends on reliable and accurate predictions of chemical toxicity. Validation of the GenAI model in toxicology ensures reliability, reproducibility, and practical applicability of its outputs to support risk assessment tasks. It helps to minimize model uncertainty using performance evaluation benchmarks. Hond et al. (de Hond et al., 2024) highlighted two main challenges in validating GenAI methods. Firstly, it is hard to quantify the outputs of GenAI for all cases. Secondly, the challenge of extensive output space. GenAI can have multiple and diverse outputs for the same problem in toxicology. For example, systems like ChatGPTs exhibit remarkable versatility in outputs within toxicological contexts, where one prompt regarding chemical hazard assessment can quickly generate many different outputs, each potentially correct for a particular scenario. This situation complicates direct comparisons with established ground truths. Therefore, benchmarking and validating GenAI models is challenging (Bandi et al., 2023). It needs to handle these complexities with chemically and biologically meaningful language.

Several GenAI's model validation metrics have been proposed, and each offers distinct insights into the models' performance to evaluate their reliability and accuracy from different perspectives (Lucic et al., 2017; Sajjadi et al., 2018; Borji, 2019; Tahmasebi, 2023; Horompoly and GenAI, 2024; Mackay et al., 2024). Fig. 20 depicts some of the critical validation landscape of GenAI models in toxicology. Qualitative Assessment depends on human experts to analyze outputs for relevancy and realism. In contrast, Quantitative Metrics use numerical measurements such as (FID, IS, Precision-Recall, etc.) to analyze the output quality. Statistical testing analyzes the model's robustness and stability. Functional Validation proves the effectiveness of the GenAI model using downstream tasks. Model decisions are validated using explainability and interpretability analysis. Further, baseline models compare the performance of the new model. Lastly, ethical and regulatory benchmarks ensure fairness, ethical standards, and regulatory guidelines. However, based on our critical literature review, we need validation benchmarks tailored to specific toxicological problems rather than a holistic view.

Table 7
Toxicological and chemical databases.

Source	Objective	Impact	AI Relation to RA	Updates & Access
PubChem (Kim et al., 2016)	Chemical molecules database	Supports chemical research	AI enhances chemical data analysis	Periodic updates Public access
TOXNET (NIH, 2023)	Toxicology and environmental database	Access to toxicological data	AI enables efficient data retrieval	
ChemSpider (Pence and Williams, 2010)	Chemical structures and data access	Aids research and education	AI assists in chemical analysis	
ECHA (Musset n. d.)	Chemical info for EU compliance	Ensures regulatory adherence	AI harmonizes regulatory data	
IRIS (Woodard et al., 2009)	Health assessments for chemicals	Policy-informing RAs	AI models enhance health RA	
TOXLINE (McHale et al., 1986);	Toxicological literature database	Supports research	AI analyzes toxicological literature	
HSDB (Fonger, 1995)	Toxicology data for hazardous chemicals	Hazard identification aid	AI uncovers toxicological insights	
CPDB (Gold et al., 1991)	Long-term animal cancer tests analysis	Carcinogenic risk information	AI assesses carcinogenic risks	
TOXRIC (Wu et al., 2023)	Comprehensive toxicological data database	Provides extensive toxicological benchmarks and data	AI facilitates comprehensive analysis and interpretation of toxicological data	

5. Benefits and Challenges

As highlighted in the discussed literature, GenAI has many opportunities to help in the advancements in toxicology. Despite this, we must navigate the complexities of GenAI, which remains a critical challenge that must be addressed to harness GenAI's true capabilities fully. In the following subsections, we discuss the benefits and challenges of GenAI in toxicology.

5.1. Benefits of GenAI in Toxicology

Applications of GenAI have numerous benefits in the field of toxicology, and these methods are better placed than their predecessors. Some of the significant benefits identified by the above literature are discussed in this section. Predictive modeling is a considerable benefit, as we can predict the toxicological profiles of new compounds by GenAI models like GANs and minimize the need for animal tests and even human trials. Toxicological properties prediction can help drug development and reduce the duration of the development process. Data generation is a remarkable ability of GenAI. Particularly in toxicology, having data for analysis and experimentation is a re-source-exhaustive problem regarding time, cost, human resources, and trial subjects. GANs can generate synthetic data, which is almost like accurate data. This means faster trails. Further, hypothetical molecules can be developed for chemical space exploration. Finding safer substitute chemicals with no or minimal adverse effects is critical to sustain-able healthcare solutions and the prime focus of industry today. GenAI can find replacements with a minimal toxic nature and explain the decision-making process, which is critical in toxicology, where we can sometimes have multiple perceptions. How-ever, we need to select the most optimal one. GenAI can do hazard assessment, dose analysis, exposure modeling, and risk categorization, as discussed in Section 2.4.5. We know how a particular chemical and formulation will behave in the natural environment. This analysis can provide optimal information on the toxic nature of drugs, chemicals, and treatments. Further, a suitable biomarker can be identified as a response. Challenges for GenAI in Toxicology.

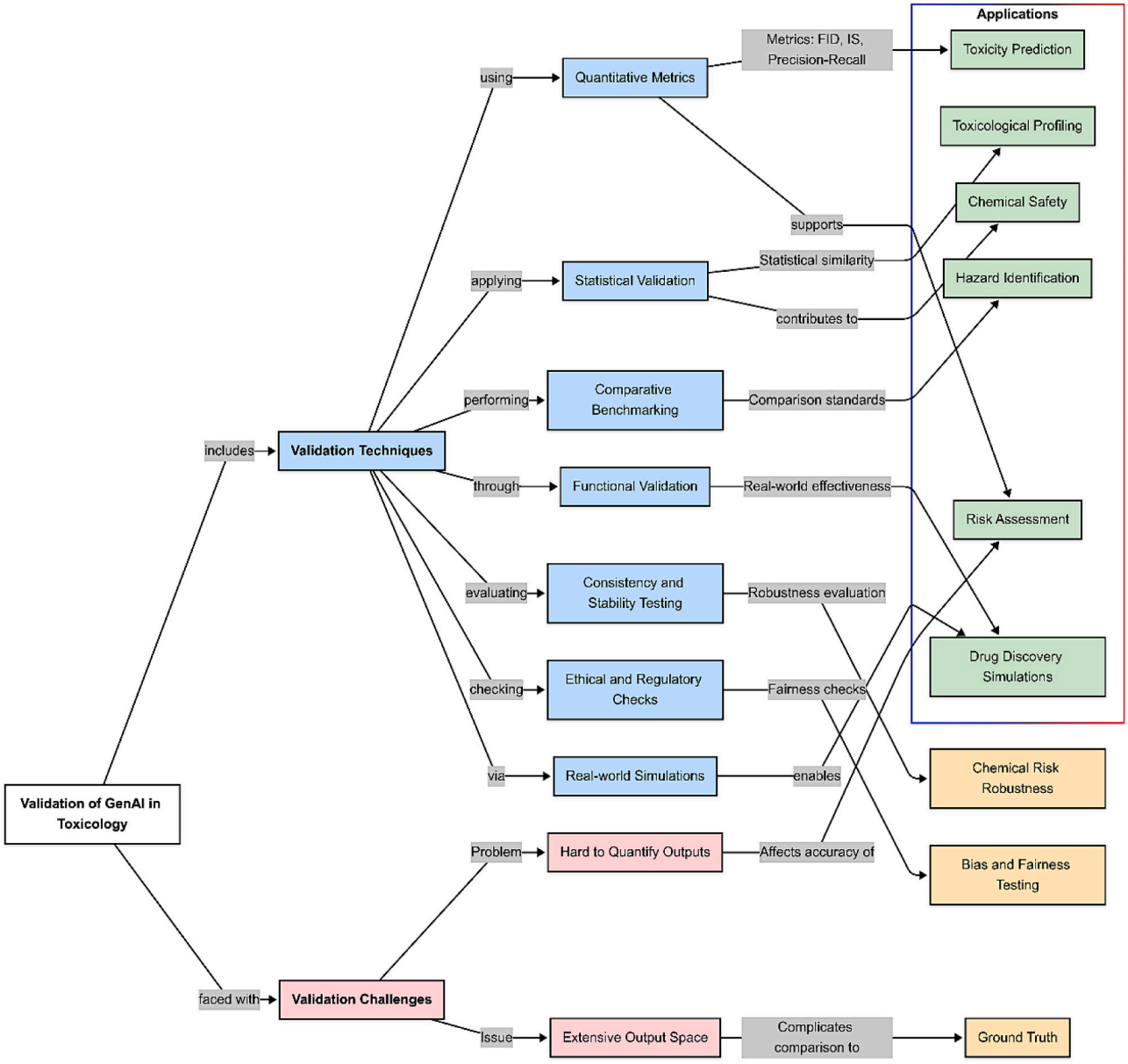

Fig. 20. Validation landscape for GenAI in toxicology.

5.2. *Challenges for GenAI in Toxicology*

Despite several promising benefits, there are some fundamental challenges that GenAI has to overcome, as discussed by Nah et al. (Fui-Hoon Nah et al., 2023) and Zhang et al. (Zhang and Boulos, 2023) in their studies. Some of the challenges identified from the above literature are discussed in this section. Data generation is discussed in Section 3 as a significant benefit of GenAI, particularly in toxicology. However, there are several challenges in data production for GenAI in toxicology, which are: (1) data quality, (2) data diversity, (3) data volume, and (4). Maintaining data quality is difficult. This makes it further essential to evaluate data re-liability and validity, as highlighted by (Zhang and Boulos, 2023). No mechanism can address these issues at this time. In toxicology analysis, it is too sensitive. Even a tiny diversion can change the outcome, meaning reliable and valid data is crucial for correct or optimal decision-making. We must be cautious when using GenAI for data generation and not ignore data production challenges. Biases in AI technologies are a big issue concerning the credibility of their outputs, as shown by Newstead et al. (Newstead et al., 2023) which ultimately affects decision-making, as highlighted by Srivastav et al. (Srivastav et al., 2023).

A significant challenge is handling uncertainties, which occurs majorly during optimization and decision-making in deep learning technologies like GenAI, which Gawlikowski et al. (Gawlikowski et al., 2023) discussed in their review. Further, Abdar et al. (Abdar et al., 2021) introduced uncertainty quantification methods for handling uncertainties. GenAI technologies have a black box dilemma, resulting in a lack of transparency and interpretability. It further leads to very limited Explainability. In the toxicology domain, the outcomes must be explained well enough for optimal decision-making (Chatterji, 2023; Caserta et al., 2023). At present, GenAI technologies have limited or confined explanation capabilities. GenAI methods are complex. They must be trained on large amounts of data with complex parameter settings (Moore, 2023; Guo et al., 2019). We need an expert who understands these technologies completely, and toxicological experts are more from natural science than AI, which is a challenge to overcome if we need to unleash the power of GenAI. To benefit from GenAI, a well-trained expert is necessary. Otherwise, outcomes can be affected badly.

Concerning the literature reviews above, especially in toxicology, this is challenging as the core domain of re-searchers is natural sciences rather than AI. We need to synchronize their expertise so they can optimally use GenAI.

One primary concern is how GenAI will adhere to toxicological ethics. A challenge is how to force GenAI users to follow toxicological ethics (Baxter et al., 2023). For example, they should not augment data whose experiments are banned, like human cloning. Toxicological data is sensitive as it may contain user profiling and personal medical information. We need to handle anonymity breaches, and GenAI technology can reveal users' identities. Consent and autonomy are other significant issues (Koerner, 2023). Major GenAI technologies and tools have untransparent consent and autonomy rules. Unlearning means the ability of GenAI to forget, disassociate, or disconnect from specific data and what they deduced from data they consumed or trained on. Integrating unlearning mechanisms with GenAI is imperative to privacy and compliance (Bae et al., 2023). However, no such mechanisms are available today. Understanding the unlearning pathway in GenAI is too complex as these deep learning-based architectures fundamentally follow a black-box approach.

6. Empowering Conversational-AI with GenAI

Empowering Conversational AI with GenAI means that conversational AI takes leverage from the power of GenAI to strengthen itself and make it more relevant to present and future applications. ChatGPT is a classic example of where empowering happens. The system generates output or feedback based on an input query. It can interact, analyze, infer, augment data, and visualize the gained knowledge (Mary Sabry Abdel-Messih, 2023). In a toxicological context, this empowerment is intriguing as it means a more comprehensive application domain to design holistic solutions using AI in toxicology (Modev, 2023; Singh, 2023). GenAI is used for toxicological prediction and drug discovery, where it depends on chemical inter-action and its effects on all organisms and the environment. By bringing Conversational, questions, conversational feedback, and explanations can be considered to simplify, modify, and understand new chemicals, predictions, and the whole toxicological discovery and profiling process (Matsler et al., 2024; Altundağ et al., 2024). Toxicology is a complex domain where developing an under-standing is critical for decision-making as there can be multiple perspectives of a single challenge. Interactive Learning and training play a vital role in this quest. For example, a prediction may be made using the GenAI method. Now, the interpretation may mean different things in different operating environments. Conversational-AI can help to train users to understand the various operational environments. Convergence empowered by GenAI will surely mean a higher degree of personalization where users can interact with the system, develop reasoning, and discuss the outcomes.

In Fig. 21, the empowering landscape of GenAI in the field of toxicology is depicted. Indeed, there are several challenges in achieving this. One central question will be how we can evaluate the accuracy. GenAI systems are complex, and empowering Conversational AI in any nature further complicates it, limiting the extent of empowerment. In toxicology, we may sometimes have multiple perspectives of treatments, drugs, and chemicals, which depend on internal biological and external environments. Now, being bias-free is a challenge. Generalization is also arduous because we may have opinions rather than decisions. With the empowerment of conversational AI, we elevate further threats to privacy and increase ethical issues.

7. Conclusion

Toxicology is a branch of science critical for the survival of living beings on this planet. Toxicology analyzes and understands the adverse effects of chemicals, compounds, drugs, and treatments on living organisms, including humans and the environment. The traditional toxicological Non-GenAI analysis, understanding, and reasoning methods are not sustainable and are too time-consuming, highly costly, resource-exhaustive, and inaccurate. AI is imperative as it prevents the above challenges of traditional toxicological analysis methods. Notably, the GenAI paradigm is promising in dealing with issues faced in toxicology. In this paper, we reviewed literature based on applications of GenAI in

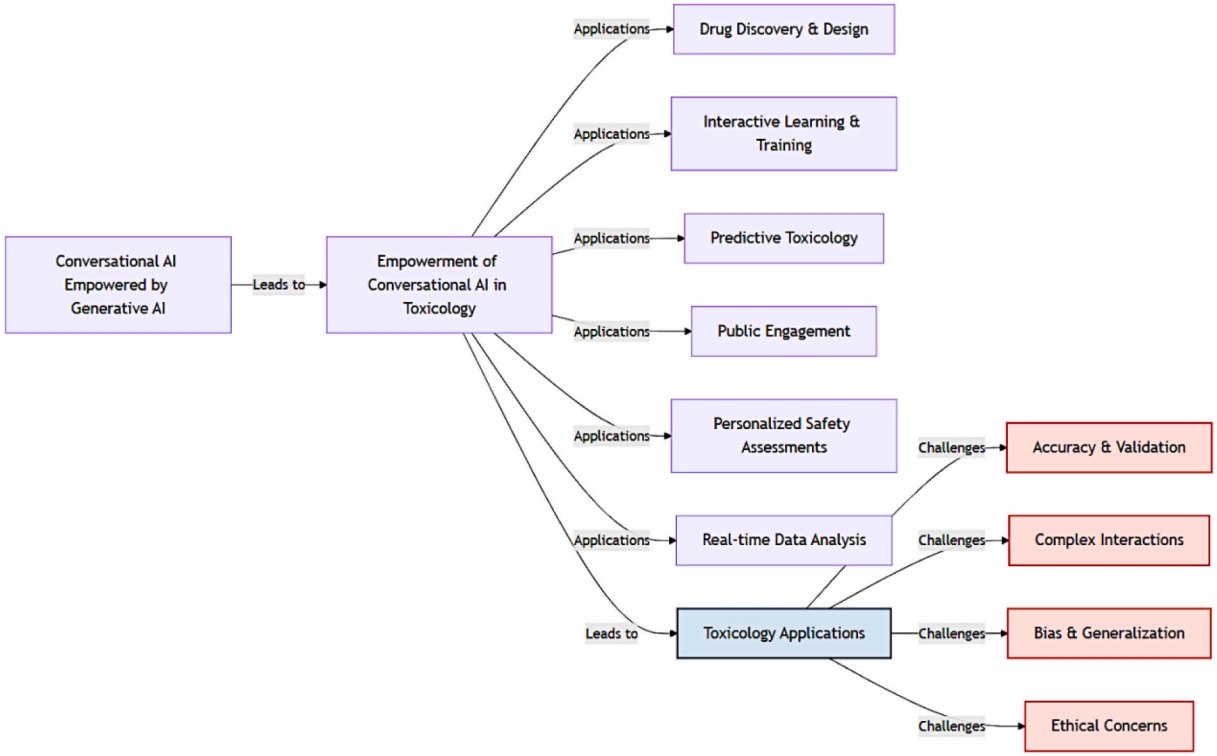

Fig. 21. Empowerment landscape for Conversational-AI with GenAI in Toxicology.

toxicology. We identified possible application classes of GenAI where their power can be unleashed to enhance our understanding of complex toxicological analysis, thus contributing to sustainable healthcare practices. These specified application classes are drug discovery, toxicological data generation, precision medicine, improved knowledge of toxicological processes, environmental toxicology, anomaly detection, Silico trials, information dissemination, educating and training (IDET) of various stakeholders, patient support, research assistance, enhanced emergency response, formulation of better public health policy, conversational AI and assisting in clinical decision-making. In addition, the paper discussed and determined which GenAI and Non-GenAI outperform each other for a particular application and where they complement each other. This review simplifies the relationship between GenAI and toxicology processes by developing intuitive figures. Further, these figures help enhance understanding of how toxicology can benefit from GenAI. The paper discussed toxicological risk assessment and management and highlighted international organizations' efforts to standardize and regulate them in these endeavors. Significant benefits and challenges GenAI faces in transforming conventional toxicology to sustainable toxicology that need to be exploited are discussed. Finally, the empowerment of Conversational AI with GenAI in toxicology is discussed. This paper can be a building block for future research endeavors on the sustainable application of GenAI to various problems in toxicology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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