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Advances in Clinical Toxicology
ISSN: 2577-4328

Transforming Toxicity Assessment through Microphysiology, Bioprinting, and Computational Modeling

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Review Article
Volume 9 Issue 1
Received Date: January 11, 2024
Published Date: February 09, 2024
DOI: 10.23880/act-16000295

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Abstract

Background: Traditional toxicity testing emphasizes animal models with growing concerns regarding predictive capacity, throughput and ethics. Rapid innovation surrounding human cell platforms, bioengineered tissues, omics techniques and computational tools offers more modern alternatives aligned with expanding knowledge of chemical biological pathways. These disruptive approaches promise immense potential to transform next-generation chemical safety assessment and drug development pipelines.

Purpose: This review provides clinical researchers an updated, comprehensive perspective across evolving areas of focus in new toxicity testing methods with analysis of latest advances and translational context.

Main Body: We survey progress in two- and three-dimensional human cell cultures recapitulating tissue/organ complexity impossible in conventional assays. Complementing this, computational modeling integrates structure-activity relationships, physicochemical properties and physiological interactions to predict pharmacokinetics and toxicity in silico. Expanding model organisms add further dimensionality and demographic relevance. High-throughput omics and imaging technologies unravel mechanisms and illuminate biomarkers undetectable by standard measures. Specialized techniques show high promise addressing toxicodynamic intricacies within disease contexts like diabetes and NAFLD. Evaluating traditional medicines and expanding phytochemicals likewise represents an area of growth well-suited for contemporary platforms. Future outlook weighs remarkable potential advantages in reducing animal testing demands, enabling precision toxicology links to clinical medicine and overhauling core chemical risk assessment frameworks.

Conclusion: This review intends to catalyze discourse on strategic optimization priorities and roadmaps towards fully unlocking the immense yet still emerging public health potential of these disruptive techniques poising transformation in toxicity sciences centered on human-focused models.

Keywords: Toxicity Assessment; Microphysiology; Bioprinting; Computational Modeling

Abbreviations: 2D: Two-Dimensional; 3D: Three-Dimensional; AI: Artificial Intelligence; MS: Mass Spectrometry; NMR: Nuclear Magnetic Resonance; NAFLD: Non-Alcoholic Fatty Liver Disease; OCT: Optical Coherence Tomography; PBPK: Physiologically Based Pharmacokinetic; QSAR: Quantitative Structure-Activity Relationship; TCM: Traditional Chinese Medicine.

Introduction

Traditional animal toxicity testing has been the standard for evaluating drug and chemical safety for decades [1,2]. However, these methods have significant limitations including being expensive, time-consuming, low-throughput, and not always predictive of human responses. This has driven the development of new techniques and models aimed at reducing, refining and replacing animal testing [3-5]. Recent advances in in vitro systems and in silico modeling have enabled more human-relevant and predictive approaches to toxicology assessment [6,7]. High-throughput screening combines automated robotic systems with libraries of human cell lines to evaluate compound effects and mechanisms of toxicity. Organ-on-a-chip microphysiological systems utilize microfluidics and human-derived tissues to emulate organ structure and function. Genome editing tools like CRISPR allow the creation of novel in vitro models with disease-specific genotypes [8-10]. Computational methods like quantitative structure-activity relationship (QSAR) models, physiologically-based pharmacokinetic (PBPK) modeling, and machine learning algorithms applied to large toxicology datasets have accelerated predictive toxicology. These in silico models provide rapid insight into compound pharmacokinetics, metabolism, and potential organ toxicities [11,12].

Additionally, induced pluripotent stem cell (iPSC) technology now enables the derivation of diverse human cell types for toxicity analysis. iPSC-derived cells better capture population diversity compared to immortalized cell lines. High-content imaging and omics profiling of iPSC-derived cells exposed to compounds provide rich phenotypic datasets for toxicity prediction [13,14]. This review comprehensively surveys emerging techniques, disease contexts, and future outlook to provide clinical researchers an updated perspective. It aims to catalyze discourse on optimization priorities and strategic roadmaps toward fully unlocking the public health potential of these disruptive approaches to better safeguard therapeutic advancement.

In Vitro and In Silico Models

In vitro and in silico models provide important alternatives to traditional animal testing for evaluating chemical and drug toxicity. These systems allow for high-throughput screening, reduce costs, and align with ethical opposition to excessive animal testing. A range of models have emerged to recapitulate aspects of human physiology and predict potential toxicities.

2D Cell Cultures

Two-dimensional (2D) cell cultures form the most basic in vitro system. These models culture human cell lines as monolayers on plastic or glass substrates. Immortalized cell lines, such as HepG2 hepatocytes and A549 lung epithelial cells, or primary cells sourced from human tissue provide human-relevant biology. High-throughput screening assays detect cytotoxicity and functional endpoints like enzyme secretion. Co-culturing with multiple cell types enables evaluation of intercellular interactions [15,16]. Limitations of 2D cultures include lack of native tissue architecture, limited lifespan of primary cells, and adaptation of immortalized lines to artificial culture conditions. Microfluidic organs-on-chips integrate multiple 2D cultures to mimic organ physiology. Nonetheless, 2D systems remain heavily used for cost-effective cytotoxicity screening due to their simplicity [17-19].

3D Organoids and Micro physiological Systems

Three-dimensional (3D) culture systems better reflect human tissue complexity. Organoids derived from stem cells self-organize into miniature organs following developmental programs. Microphysiological systems position cells in 3D configurations using scaffolds, 3D printing, and microfluidics. These enhance resemblance to tissue-level architecture and function [20-23]. For instance, liver microtissues array hepatocytes with stromal cell types into sinusoid-like structures condusive to drug metabolism and toxicity. Intestinal organoids model distinct segments of the gastrointestinal tract on chips with peristaltic motion and fluid flow. Assembly of multiple organoids on integrated microfluidic devices enables evaluation of inter-organ interactions [24,25]. Beyond organ-level complexity, advantages include primary human cell integration, perfusable vasculature, and culture longevity exceeding months. Limitations persist in fully recreating tissue heterogeneity and accurately reflecting human pharmacokinetics. Ongoing advances in tissue engineering continue progressing physiological relevance [26].

Computational Models

In silico computational models provide alternatives to experimental assays. These predict pharmacokinetic behavior and potential toxicities using machine learning, physicochemical properties, and biological interactions.

QSAR Models

Quantitative structure-activity relationship (QSAR) models correlate chemical descriptors with bioactivities using statistical regression. These predict toxicity endpoints for untested chemicals based on structure similarities with compounds having known effects [27]. QSAR models now exist predicting mutagenicity, carcinogenicity, developmental/reproductive toxicity and other effects. For example, DEREK Nexus contains dozens of toxicity QSAR models derived from curated data on over 6,000 compounds. Limitations of QSAR models include reliance on existing data, applicability domains restricting chemical space, and inadequate capture of mechanisms [28].

PBPK Models

Physiologically based pharmacokinetic (PBPK) modeling simulates ADME (absorption, distribution, metabolism and excretion) using prior drug physicochemistry and physiological parameters. These compartmental models represent organs/tissues with blood circulation connecting them [29]. PBPK enables prediction of chemical concentrations in various organs over time. This facilitates estimating dose exposures and tissue dosimetry to evaluate potential toxicity. Used earlier in development than human trials, PBPK models guide dose selection and mitigate toxicity risks. However, requirements for comprehensive parameterization remains a challenge [30,31].

AI for Toxicity Prediction and Modeling

Artificial intelligence, especially deep learning, is gaining rapid traction for toxicity evaluation. AI algorithms train on large chemical datasets to predict potential toxicities with high accuracy. Models include recurrent neural networks, graph neural networks integrating molecular structure, and hybrid approaches combining AI with PBPK modeling [32]. Key examples include AstraZeneca's liver toxicity models, QuantumBlack's Mutagenesis ML and OrganTox AI models, and the META framework integrating gene expression data. Multiple startups now provide predictive toxicity services. Benefits center on performance exceeding other in silico methods and capacity for integrating diverse data types. Cautions remain around model interpretability and bias in training data. Regulatory acceptance has slowly increased but still varies widely [33,34]. Looking ahead, collaborative public-private data sharing efforts will expand available training data to power next-generation AI models. Incorporating more causal biological mechanisms is expected to enhance model generalizability and trust. While unable to fully replace experimental toxicity testing, usage of AI models continues growing to better predict potential toxic liabilities early in development (Table 1) [35,36].

Method	Description	Advantages	Limitations
2D cell cultures	Human cell lines cultured as monolayers	Simple, cost-effective for cytotoxicity screening	Lack native tissue architecture, limited lifespan of primary cells
3D organoids	Self-organized miniature organs from stem cells	Mimic tissue complexity, architecture, and function	Do not fully recreate tissue heterogeneity and human pharmacokinetics
Organs-on-chips	Cells arranged in 3D using microfluidics	Perfusable vasculature, co-culture of multiple cell types	Still simplifications of true tissue physiology
QSAR models	Predict toxicity based on chemical structure-activity relationships	Rapidly predict toxicity for untested chemicals	Reliant on existing data, limited applicability domains
PBPK models	Simulate ADME using physicochemistry and physiology	Predict tissue exposures and dosimetry	Require comprehensive parameterization
AI models	ML algorithms predict toxicity from large datasets	High accuracy exceeding other in silico methods	Challenges with model interpretability and bias

Table 1: New Toxicity Testing Methods.

Novel Model Organisms

Expanding the diversity of model organisms provides improved representation of human biology absent in traditional animal models. These novel systems allow new perspectives on pathways underlying toxicity susceptibilities.

Zebrafish

Zebrafish have emerged as a key higher-order toxicity model owing to evolutionary conservation with mammals and compatibility with high-throughput testing. Embryonic zebrafish offer a rapid vertebrate development model to assess teratogenicity through the first 5-7 days of embryogenesis.

Toxicity screening platforms leverage automated imaging to detect morphology changes in zebrafish larvae following chemical exposure [37,38]. Adult zebrafish additionally model chronic disease processes. Studies have evaluated chemical impacts on behavior, reproduction, cardiovascular function among other endpoints [39,40]. Transgenic zebrafish with reporter genes facilitate non-invasive tracking of biological responses. Limitations of zebrafish include partial representation of mammalian physiology given evolutionary divergence. Nonetheless, integration with other model systems helps strengthen mechanistic inferences [41].

Humanized Mice

Mice engrafted with functional human cells or tissues provide improved preclinical models combining whole-organism complexity with human biology. Multiple approaches exist: CD34+ hematopoietic stem cells enable human immune system reconstitution in immunodeficient mice. Primary tissue transplantation facilitates assessment of toxicity responses in human neural, hepatic, pancreatic and other cell types in vivo [42-44]. Beyond direct tissue integration, CRISPR knockin of human genes related to drug metabolism improves correspondence of xenobiotic responses. Humanized mouse models thereby increase clinical translational relevance over tradition mouse strains in multiple areas including immunotoxicity. Expense and technical demands constrain widespread usage though innovations may increase accessibility [45-47].

Human Gut Microbiota

The human gut microbiome mediates chemical exposure through ingestion, influencing metabolic fate and subsequent bioactivities. Interspecies variation in gut microbes contributes to differences in chemical toxicities across model systems. Integrating representative human microbiota into preclinical testing better recapitulates physiological reality [48-51]. Illustrates the various roles performed by the gut microbiota. These include the generation of secondary bile acids (BAs) and the breakdown of proteins, as well as the breakdown of foreign substances (xenobiotics) and the synthesis of water-soluble vitamins. The gut microbiota also plays a significant role in regulating inflammation and immune responses, and it contributes to the preservation of the integrity of the intestinal barrier [52].

Approaches include colonizing gnotobiotic animals with defined microbial communities, supplementing in vitro cultures with probiotics, and computational integration into PBPK modeling [53]. The MIDI-Health platform allows high-throughput chemical testing on primary human fecal cultures. Accounting for microbiome-mediated metabolism promises to improve accuracy particularly for orally-administered drugs and environmental contaminants [54].

Omics Approaches

Omics technologies measure global biomolecular changes occurring with toxicity exposures. These unravel mechanisms of compound interactions and new biomarkers for hazard identification.

Genomics

Genomic sequencing identifies associations between gene polymorphisms and toxicity susceptibility. Genome-wide association studies uncover genetic risk factors in pathways regulating detoxification, DNA repair, immune activation among others based on adverse outcomes or exposure biomarkers across large cohort studies. High-throughput toxicogenomic screening directly evaluates chemical impacts on global gene expression changes [55,56]. For instance, the TG-GATES database houses liver gene expression profiles across 170 compounds to serve as reference controls. DNA microarrays rapidly profile transcriptional changes revealing mechanisms and biomarkers of organ injury not discernable from traditional endpoints [57].

Epigenomics

Epigenetic changes to DNA and histones influence downstream gene regulation relevant to chemical exposures. Toxicants directly or indirectly affect epigenetic processes like DNA methylation, histone modifications and non-coding RNA expression. High-throughput sequencing defines epigenetic alterations and illuminates new toxicity pathways missed by purely genetic approaches [58]. Notable examples linking toxic exposures and epigenetic changes include air pollution-induced respiratory effects, arsenic carcinogenesis mechanisms and transgenerational impacts of certain pesticides. Ongoing integration of epigenomic data promises to provide unique insights into previously cryptic connections [59].

Metabolomics

Metabolomic analyses quantify global metabolite changes in biofluids, offering a functional readout of physiological status responsive to toxic challenges. NMR spectroscopy and mass spectrometry provide broad metabolite detection used to model biofluid metabolite signatures of exposures and early toxicity manifestations [60]. Repeat dose studies reveal metabolite trends tracking with histopathological progression. Models can diagnose onset of organ injury (e.g. liver, kidney) days to weeks sooner than current panels, enabling earlier intervention. Metabolic biomarkers likewise show utility for chemical risk assessment [61].

Imaging Techniques

Imaging modalities longitudinally visualize anatomical and functional impacts of toxicity non-invasively over the lifespan of a model organism. These provide complementary data on emergent macroscale changes not always predictable from cell assays.

Ultrasound Imaging

Ultrasound visualizes structure and blood flow in soft tissue without ionizing radiation. High-frequency ultrasound enables detailed assessment of tissue architecture in skin, eye, kidney, cardiovascular and other organs. Micro-ultrasound further achieves cellular resolution to visualize early histopathological changes from toxicant exposures in vivo [62]. Ultrasound biomicroscopy, for example, achieved precise 3D imaging of embryo abnormalities in zebrafish development toxicity studies. Contrast enhanced ultrasound improves sensitivity and multiplexing capacity. Portability, cost-effectiveness and lack of toxicity makes ultrasound imaging widely accessible for longitudinal toxicology [63].

Optical Imaging

Optical reporters including bioluminescent proteins and fluorescent labels provide sensitive dynamic readouts of cell viability and function in vivo. Bioluminescent ATP assays detect real-time cytotoxicity in target organs. Fluorophore-coupled probes enable tracking of tissue-specific processes like kidney glomerular filtration and liver biliary excretion [64]. Light sheet fluorescence microscopy offers rapid 3D imaging data without tissue processing artifacts. Optical clearing expands depth penetration and whole body imaging. Continued development of targetable optical sensors and smarter image analysis algorithms promise to transform in vivo imaging for toxicology [65].

Traditional Medicine and Herbal Toxicity Screening

Traditional medicine systems including Chinese, Ayurvedic and other ethnomedical practices use herbal formulations for therapeutic intent. As adoption of evidence-based holistic care models expands globally, evaluating safety and toxicity of these natural products grows in importance.

Traditional Chinese Medicine

Traditional Chinese medicine (TCM) relies on plant, animal and mineral materia medica prescribed in carefully balanced formulas to stimulate healing responses. TCM holds a strong presence as standard medical care in China and influences healthcare across Eastern Asia and internationally. However, variable manufacturing quality and toxic adulterants can lead to safety issues [66,67]. Hepatotoxicity, nephrotoxicity and embryonic defects number among reported adverse effects. Examples include aristolochic acid-mediated kidney disease, aconite alkaloid toxicity, and anticholinergic effects of certain formulations. Contaminants like heavy metals in mineral ingredients may accumulate over long-term use. Due to frequently lacking label transparency and individual variability in responses, granular assessment is needed to define toxicity liabilities [68,69]. High-throughput approaches show initial promise evaluating TCM product safety. Testing across >2,500 TCM extracts revealed low rates of mutagenicity, improving confidence in general genotoxic potential. However, the vast array of possible formulation combinations makes comprehensive testing infeasible. Advancing personalized prediction models and pharmacovigilance efforts tailored for TCM remain critical to ensure consumer safety amidst growing use globally [70,71].

Ayurvedic Medicine

Ayurveda represents a cornerstone of traditional Indian medicinal practice, encompassing diet, lifestyle and multi-component herbal formulations to restore wellbeing. In recent decades, interest in Ayurvedic approaches has accelerated in India, wider South Asia and abroad. With this has come enhanced focus on evaluating toxicity risks of commonly used Ayurvedic herbs [72,73]. Documented adverse effects include nephrotoxicity, hepatotoxicity, lead poisoning and arsenicosis linked to certain plant ingredients and mineral additives. Examples such as aristolochic acid nephropathy have raised international concern. Lack of consistent manufacturing standards contributes to contamination prevalence in certain market segments. Sensitive subpopulations like pregnant women and children face particular exposure risks needing further research [74,75].

Potential Toxicity of Herbal Extracts

Beyond codified traditional medicine systems, herbal extracts from roots, leaves, seeds and fruits form a prevalent and expanding segment of dietary supplements and natural health products globally. Though perceived as intrinsically safe given natural origins, many commonly used botanical ingredients have unclear toxicity profiles at different dose exposures [76,77]. Pyrrolizidine alkaloids offer prime examples of potentially toxic natural phytochemicals requiring safety evaluation, found broadly across >6000 plant species including many popular herbs and teas. Hepatotoxic, pneumotoxic, genotoxic and carcinogenic effects are reported for certain pyrrolizidine alkaloids. Content ranges substantially by plant type, growing conditions and processing, complicating risk assessment

[78]. Other concerning bioactives include estragole in fennel and basil, safrole in sassafras, aristolochic acids in butterfly ginger relatives, and furanocoumarins in figs. Extract high-throughput bioactivity profiling combining NMR, MS and AI prediction models better defines biological risks to focus tiered testing priorities [79]. Addressing the tremendous chemical diversity of phytochemicals still poses major challenges for preclinical toxicity analysis. Cross-sector efforts advancing computational toxicology methods, biologically relevant exposure models and smarter endpoints tracking key toxicity pathways will provide faster assurance on safety of emerging herbal products.

Applications in Specific Disease Areas

Leveraging next-generation toxicology methods in disease-specific contexts enhances clinical translation and personalization. Human cell models, microphysiology systems, imaging biomarkers and computational models better predict individual risk variations from standard animal data. Focus areas benefiting most from advanced testing methods include liver disease, kidney disease, diabetes, cardiovascular toxicity, infection models, and oncology.

Liver Diseases

The extensive role of liver in xenobiotic metabolism and resultant pathogenesis makes it a central focus of toxicity analysis. Advanced testing techniques provide improved models of human susceptibility variations and clinical endpoints. Primary human hepatocyte cultures better represent interindividual differences in expression of metabolic enzymes (e.g. Cytochrome P450s) and transporters relative to immortalized cell lines. Microfluidic liver chips with flow/perfusion increase functional longevity, allowing chronic toxicity evaluation. Multi-omics biomarkers from these systems deliver poised indicators of emerging liver injury [80-88]. In silico modeling simulates patient-specific pharmacokinetics and mechanistic toxicity pathways in non-alcoholic fatty liver disease (NAFLD). Imaging methods like ultrasound elastography noninvasively diagnose and track fibrosis progression. Overall these approaches refine chemical risk assessment and therapeutic interventions for liver disease subgroups [89-92].

Glomerulonephritis

Glomerulonephritis represents inflammation and damage to the kidney's filtration units. Certain toxins directly instigate glomerular injury while environmental factors may trigger autoimmunity attacking the glomeruli [93]. Human kidney organoids self-developed from stem cells provide native architecture to model toxin filtration and nephrotoxicity absent in other cultures. Exposure alongside human immune cells evaluates potential antigen formation triggering autoimmune kidney reactions. Microfluidic filtration chips offer further insights into functional impairments including proteinuria and blood cell clogging at the glomerulus [94-96]. In silico modeling based on clinical glomerulonephritis biomarkers assists prediction of nephrotoxic potential. Ultrawide-field fluorescence imaging efficiently tracks glomerular filtration activity using exogenous reporters. Altogether these systems advance toxicity prediction and monitoring for personalized therapeutics development [97].

Diabetes

Diabetes markedly increases sensitivity toward drug- and chemical-associated organ damage, partially linked to underlying inflammation and vascular dysfunction. Improved toxicity models in diabetic contexts are imperative to guide appropriate risk management. Islet organoids derived from human stem cells mimic functional responses of key cell populations to better understand beta-cell health impacts. Microfluidic pancreas-on-a-chip with tri-culture of endocrine, exocrine and endothelial cells boosts clinical relevance. High-content imaging tracks beta-cell death dynamics following exposure. Multi-tissue chips interconnected with vascular flow assess system-level end-organ effects [98]. Furthermore, PBPK modeling incorporating diabetes-associated co-morbidities and polypharmacy predicts exacerbated exposure and adverse reactions. AI algorithms analyze patient phenotypes and retinal imaging biomarkers to tailor compound testing in pertinent diabetic cohorts. Overall, advanced approaches deliver improved preclinical screening to balance therapeutic need with disease-specific toxicity risks [99-102].

Cardiovascular Toxicity

Drug-induced cardiovascular liabilities remain leading causes of compound failure and market withdrawal. Sophisticated models profiling electrical, functional and structural effects better predict arrhythmia, thrombosis and blood pressure risks [103,104]. Human induced pluripotent stem cell derived cardiomyocytes exhibit appropriate electrophysiological features for high-throughput arrhythmia safety screening. Multi-parameter readouts enhance detection sensitivity to ion channel modulators. Microfluidic vascular replicas reconstituted with endothelial, smooth muscle and perivascular cells assess thrombosis mechanisms absent in cell cultures [105,106]. Moreover, PBPK modeling assimilates clinical risk factors like diet and age for enhanced exposure simulation in vulnerable groups. Echocardiography, OCT and MRI imaging quantify myocardial strain dynamics and perfusion changes indicating early pathogenesis prior to overt symptoms [107].

Breast Cancer

Breast cancer subgroups display differential therapeutic toxicity risks contingent on hormonal and genomic phenotypes. Improved modeling of this heterogeneity promises more precise management of adverse drug reactions [108]. 3D breast cancer organoid arrays preserving tumor architecture, microenvironmental factors and genetic diversity better recapitulate drug responsiveness distinctions across molecular subtypes than conventional 2D cultures. Multiplex pharmacogenomic biomarker readouts assist precision risk screening [109,110]. Further incorporating stromal elements like cancer-associated fibroblasts refines accuracy of treatment response projections based on the genomic landscape. Enhanced biobanks leveraging these techniques will expand cohorts for uncommon subgroups to derive sufficient statistical power for clinical translation (Table 2) [111,112].

Colorectal Cancer

Toxicity issues also burden colorectal cancer therapeutics, spurring development of enhanced modeling approaches. Multi-region tumor organoid biobanks better represent intratumoral heterogeneity in genetics and microenvironment interactions determining regional chemosensitivity [113-115].

Disease Context	Advanced Testing Methods
Liver disease	Primary human hepatocytes, liver microtissues, multi-omics biomarkers, ultrasound elastography
Kidney disease	Human kidney organoids, microfluidic filtration chips, computational modeling of clinical biomarkers
Diabetes	Islet organoids, tri-culture microfluidic pancreas chips, PBPK modeling with diabetes co-morbidities
Cardiovascular	hiPSC-derived cardiomyocytes, vascular microfluidics, echocardiography, OCT, MRI
Breast cancer	3D tumor organoid arrays, stromal co-cultures, pharmacogenomic profiling
Colorectal cancer	Multi-region tumor organoid biobanks

Table 2: Toxicity Evaluation in Specific Disease Contexts.

Future Outlook

Ongoing progress in new toxicity testing methods is poised to transform chemical safety assessment, therapeutic screening, and basic mechanistic research in the years ahead. Key opportunities center on reducing animal testing demands, enabling precision toxicology bridges to clinical medicine, and overhauling human health risk assessment.

Opportunities for Reducing Animal Testing

Evolving beyond traditional animal models promises significant ethical and economic dividends. Expanding utilization of non-animal systems addresses rising ethical concerns, directives like Europe's ban on cosmetic testing in animals, and wider adoption of 3R principles targeting replacement, reduction and refinement of animal use [116]. In addition, next-generation platforms enhance efficiency for drug developers facing swelling preclinical costs and timeline pressure. Increased throughput, multiplexing capacity and longitudinal assessment in microphysiological organ chips and bioengineered tissue surrogates facilitates more rapid compound pipeline screening [117,118].

Precision Toxicology and Personalized Medicine

Burgeoning techniques also provide tools to advance precision toxicology in alignment with the wider personalized medicine movement. Human biomimetic platforms, diverse model organisms, biobanks and bioprinted tissue replicates allow interrogation of individual risk susceptibility variations impossible in animal models. High-parameter omics profiling and computational modeling integrate unique genetics, physiology and exposure factors toward sharply customized risk projection. As healthcare increasingly embraces molecular phenotyping for tailored interventions, parallel adoption in toxicology spheres can link environmental influences with biomarker shifts predictive of future disease onset [119].

Improved Human Health Risk Assessment

Broader integration of contemporary toxicity evaluation systems promises to strengthen chemical risk analysis applied in public health policy. Replacements for guideline animal studies enable more rapid and economical assessment of industrial chemicals, pesticides, consumer product ingredients and contamination threats [120]. High-throughput platforms facilitate evaluation of cumulative impacts from the vast array of real-world environmental mixtures absent from single chemical testing. Enhanced exposure modeling assimilating human activity patterns and demographic factors provides sharper projections of population-level risks [121].

Conclusion

This review comprehensively surveys the landscape of emerging techniques advancing the field of toxicity testing and evaluation. High-throughput human cell platforms, microphysiological systems, and bioprinted organ proxies offer more predictive alternatives to traditional animal models. Expanded model organisms, imaging modalities, omics profiling, and computational modeling provide multifaceted assessment of exposure impacts on tissue structure and function over time. Application in disease contexts like diabetes, liver disease, and cancer promise improved clinical translation of toxicity findings to enable precision risk assessment tailored to individual genetic and physiological factors. Taken together, these disruptive approaches are poised to transform chemical safety evaluation, therapeutic screening, and foundational knowledge of biological pathways mediating environmental influences on human health.

Recommendations

Realizing the full potential of new toxicity testing methods will require cross-sector collaboration to systematically validate performance and optimize integration. Expanded chemical safety databases incorporating human-specific findings should catalyze regulatory acceptance and overhaul of risk analysis frameworks centered on animal studies. Strategic investment is needed to enhance accessibility of advanced platforms for academic researchers and small companies through shared facilities and open-access biobanks. Educational initiatives can strengthen next-generation toxicology expertise emerging at the interface of tissue engineering, genetics, computing and clinical medicine. Overall, harnessing toxicity testing innovations promises immense dividends for environmental health, drug development, and the wider personalized medicine movement, warranting coordinated efforts to accelerate progress.

Availability of Data and Materials

All data are available and sharing is available as well as publication.

Competing Interests

The authors hereby that they have no competing interests.

Funding

Corresponding author supplied all study materials. There was no further funding for this study.

Author's Contributions

The authors completed the study protocol and were the primary organizers of data collection and the manuscript's draft and revision process. Tamer A. Addissouky wrote the article and ensured its accuracy. All authors contributed to the discussion, assisted in designing the study and protocol and engaged in critical discussions of the draft manuscript. Lastly, the authors reviewed and confirmed the final version of the manuscript.

Acknowledgements

The authors thank all the researchers, editors, reviewers, and the supported universities that have done great efforts on their studies. Moreover, we are grateful to the editors, reviewers, and reader of this journal.

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