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Advances and challenges in modelling the environmental fate and exposure of pharmaceuticals: a comprehensive review

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Pharmaceutical contamination in the environment poses a global concern, raising questions about potential implications for both ecology and human health. Unravelling the fate and exposure of these contaminants is crucial, as it depends on various factors, including their physicochemical properties, metabolic pathways, breakdown processes (*e.g.*, oxidation and hydrolysis), and environmental conditions. Applying model-based approaches to assess the fate and exposure of pharmaceuticals is essential for evaluating their potential risks and impacts on the environment and public health. This paper reviews the state-of-the-art models used to predict the environmental fate and exposure of pharmaceuticals, focusing on sources, theoretical frameworks, comparative analyses of existing models, and factors such as polarity, metabolism, and breakdown processes. Additionally, the paper identifies current challenges and outlines future directions in this field.

Environmental significance

Pharmaceutical contaminants represent a global environmental concern, impacting both ecosystems and human health. Understanding their fate and exposure is essential for risk assessment and management. This work critically evaluates current modelling approaches for predicting pharmaceutical behaviour in the environment, highlighting key limitations such as simplified assumptions regarding complex environmental interactions, limited degradation data, and incomplete bioaccumulation predictions. Addressing these challenges through more sophisticated mechanistic insights, enhanced data collection, and integration of machine learning methods provides immediate benefits. These improvements will significantly enhance predictive capabilities, support more accurate environmental assessments and inform targeted mitigation strategies to safeguard ecosystems.

1 Introduction

The widespread use of pharmaceuticals for human and veterinary health has improved agricultural productivity and quality of life for millions of people around the world. However, the increasing production and consumption of pharmaceuticals also pose a potential threat to the environment. Most of these substances are only partially removed or transformed during the wastewater treatment processes and subsequently enter aquatic and terrestrial ecosystems.[1] This is a potential health risk to the organisms exposed to these pharmaceutical residues, and also potentially to humans who are exposed to them in the food chain or *via* drinking water. Due to a developing understanding of their environmental behaviour and a lack of regulation governing their occurrence, fate, and effects,[2] pharmaceuticals are classified as emerging contaminants.[3]

The fate and exposure of pharmaceuticals in the environment depend on various factors, including their physicochemical characteristics, metabolic processes, degradation processes, environmental conditions, and sources of exposure.[4] These factors influence their distribution, persistence, bioaccumulation, and bioavailability in different environmental compartments like soil, sediment, surface water, and groundwater. The exposure of pharmaceuticals to organisms and humans can lead to adverse effects such as antimicrobial resistance (AMR), altered behaviour[5] and mortality.[6]

Modelling the fate and exposure of pharmaceuticals in the environment helps to assess the potential risks and impacts of these contaminants on the environment and human health. Modelling allows us to gain information about the sources, transport, concentrations, and trends of pharmaceuticals in the environment, along with the uncertainty and variability associated with these parameters. Modelling can also provide predictive insights to support the development and evaluation of mitigation measures, such as improved wastewater treatment, source control, and environmental monitoring. Furthermore, it can be used to assess the impact of environmental and societal change on pharmaceutical pollution. While other model review papers have focused on the broader theme of contaminants in the environment,[7–9] there is a notable gap in the literature specifically focusing on pharmaceutical exposure

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models. By contrast, a targeted synthesis on pharmaceutical exposure models remains limited, with most contributions being model-specific descriptions.[10–12] This lack of targeted reviews is considerable, considering the unique and complex nature of pharmaceutical contaminants.

While modelling provides invaluable decision support by organising evidence and projecting plausible environmental concentrations and exposures, it is not definitive. Model precision is limited by its structure, parameter uncertainty (*e.g.*, ionisation-dependent sorption and degradation), and data gaps, especially for organic bases and transformation products. These limitations demand a purpose-driven model selection and transparent communication of uncertainty. Therefore, models are framed as testable hypotheses whose predictions should be complemented with targeted monitoring and sensitivity/uncertainty analysis, rather than as exact representations of reality.

This paper aims to bridge the existing gap in the literature by providing a comprehensive review of the current state-of-the-art in modelling pharmaceutical fate and exposure in the environment. The key focus areas of this review are to: identification and quantification of sources of pharmaceutical contaminants (*e.g.*, pharmaceutical manufacturing, healthcare facilities, households, agriculture); explore the theoretical framework of fate and exposure modelling; conduct a detailed analysis of fundamental studies with an emphasis on various modelling types; and examine how different environmental media (*e.g.*, soil, water) influence the fate and transformation of pharmaceuticals. For the purposes of this review, the term "breakdown processes" is used to encompass various mechanisms, including oxidation, photodegradation, hydrolysis and biodegradation, ensuring a comprehensive understanding of the transformation pathways of pharmaceutical compounds in the environment. Pharmaceuticals warrant a focused synthesis because they are intentionally bioactive at low doses, often ionisable with speciation-dependent fate and bioavailability, and frequently generate bioactive transformation products—features that distinguish them from broader contaminant classes and shape both model structure and data needs.

2 Methodology

The methodology of this review involves a systematic search and analysis of the existing literature related to the modelling of pharmaceutical fate and exposure in the environment. Peer-reviewed articles and other relevant publications were reviewed to gather information on several modelling approaches, their underlying assumptions, and their applicability to different environmental scenarios. The search was conducted by using PubMed, Scopus, Google Scholar, and Web of Science. The search string comprised of terms related to pharmaceuticals fate and exposure modelling ("pharmaceuticals" OR "drugs") AND ("fate and transport" OR "environmental fate" OR "exposure modelling" OR "exposure assessment") AND ("modelling tools" OR "modelling approaches" OR "simulation models" OR "computational models")

Fig. 1 shows a schematic of the review process. The initial search yielded a considerable number of articles. The literature was first screened by their titles and abstracts to determine their relevance to the study's objectives. After this preliminary screening, the full texts of potentially relevant articles were closely examined to establish their suitability for inclusion in our review. The search was confined to articles published in

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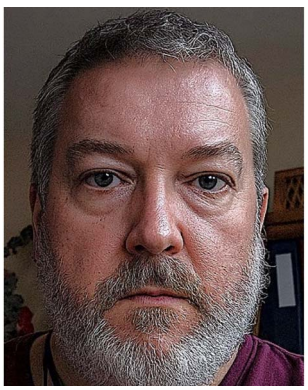

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Stephen Lofts has worked at the UK Centre for Ecology and Hydrology as a Soil and Aquatic Chemist for 30 years. His main interests are in the use of chemical process knowledge to understand and predict chemical fate, bioavailability and environmental impacts. His past research has focused on metals and nanoparticles and is currently expanding to consider organic chemicals such as pharmaceuticals, pesticides and PFAS.

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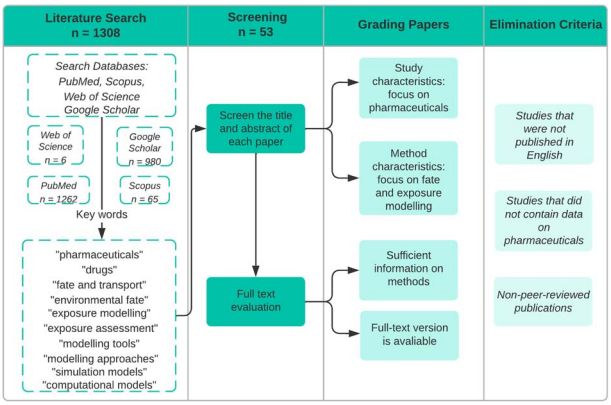

Fig. 1 Schematic representation of the review methodology.

English. Moreover, non-peer-reviewed reports or studies that did not relate specifically to pharmaceuticals were excluded. The analysis also involved a critical evaluation of the methodologies employed in these studies, focusing on their strengths, limitations, and potential for future improvements.

3 Pharmaceutical contamination: sources, overview, and impact

The widespread use of pharmaceuticals for both human and veterinary purposes has led to their release into the environment through various pathways. This extensive presence of pharmaceuticals in water[12] and soil[13] poses a global issue potentially impacting ecological systems and human health over the long term. The presence, concentration, and patterns of these pharmaceuticals in the environment are influenced by factors such as the types and quantities of pharmaceuticals manufactured, used, and discarded, alongside environmental conditions and dynamics.

This section identifies and analyses the primary sources that contribute to the presence of pharmaceuticals in the environment. This encompasses the processes involved in pharmaceutical manufacturing, the role of healthcare facilities, residential areas near drug sources, and agricultural practices. Additionally, the article examines different sources and their effects on pharmaceutical contamination levels and exposure. It also studies regulatory measures that could be implemented to manage such contaminants and explore global trends in pharmaceutical pollution.

3.1. Overview of pharmaceutical contamination and primary sources

Sources of releases of pharmaceuticals to the environment include direct emissions from drug manufacturing, patient and animal excretion into sewer and wastewater treatment systems or direct to the environment, aquaculture activities, and disposal of unused or expired medicines.[14,15] Fig. 2 represents

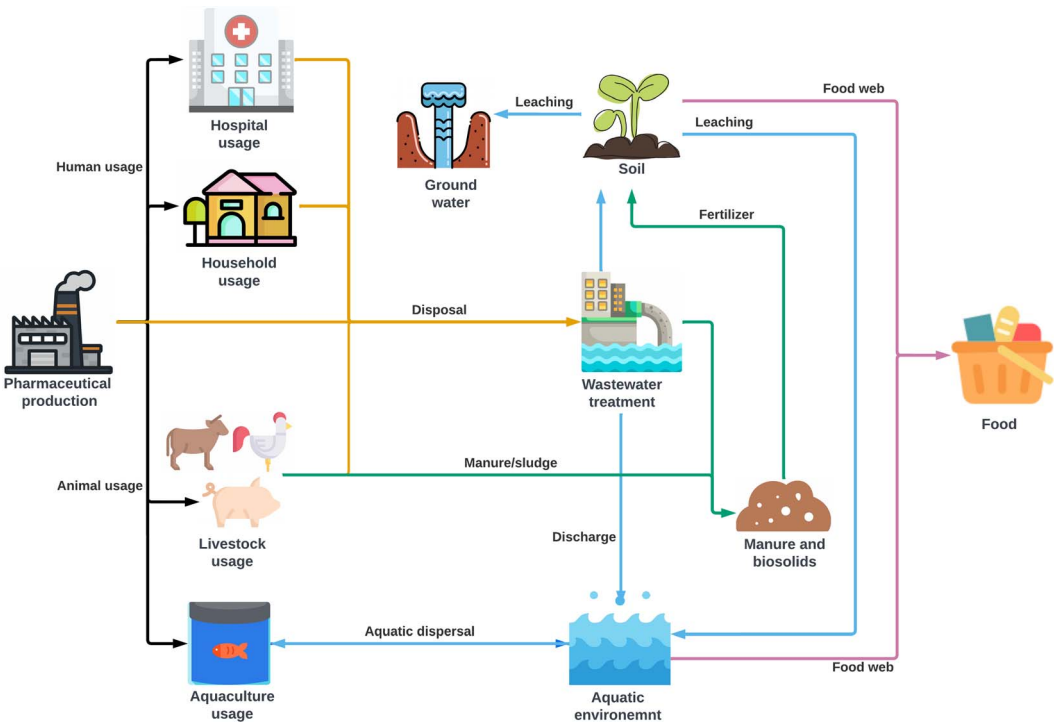

Fig. 2 Environmental emission pathways of pharmaceuticals: this diagram illustrates how pharmaceuticals are emitted to the environment through various pathways. The direct discharge from pharmaceutical manufacturing facilities often ends up in wastewater treatment plants. These pharmaceuticals are consumed by humans in residences and hospitals, as well as by animals in veterinary contexts like livestock and aquaculture. Pharmaceutical usage is processed through wastewater treatment plants. The diagram uses a colour-coding scheme to denote different pathways: black for direct usage from production, orange for human impacts through sewage treatment plants (STPs) and for waste discharge and transmission *via* manure and sludge, light blue for aquatic dispersal, and purple for direct food incorporation.

the major sources of pharmaceuticals to the environment. It is widely regarded that the major source of pharmaceuticals entering the environment is *via* human and veterinary usage and disposal.[16,17] Household contributions to pharmaceutical contamination arise from the excretion of metabolised or unmetabolized drugs, as well as the improper disposal of unused or expired medicines in waste.[18] The use of veterinary pharmaceuticals for animal health and growth, as well as the utilisation of manure and biosolids as fertilisers on crops and lands, leads to the exposure of antibiotics, hormones, and other pharmaceuticals to the soil and water ecosystems. This contamination can impact the microbial communities, organisms, and the wider food web.[19] Pharmaceutical manufacturing is another major source of pharmaceutical contamination,[20] especially locally near manufacturing facilities and in countries where environmental regulations are poorly enforced. This issue is prevalent in countries like India and China, where most of the global active pharmaceutical ingredients (APIs) are produced,[21] and high concentrations of antibiotics and other pharmaceuticals have been detected in surface waters and sediments near manufacturing facilities.[22] Hospitals and healthcare facilities are also important sources of pharmaceutical contamination, as they manage and dispose of large quantities of pharmaceuticals, some of which are cytotoxic or radioactive.[23]

A study analysing a global database of Measured Environmental Concentrations (MECs) calculated the most frequently documented emission pathways for pharmaceuticals. Despite source information being available for only 13% of the database entries, the analysis identified a clear hierarchy of sources.[24] The study found that urban wastewater is the most dominant emission pathway, a direct result of widespread domestic use and excretion. Hospitals were calculated to be the second most common point source, discharging a multitude of pharmaceuticals at high concentrations into municipal sewage systems. Animal husbandry was ranked as the third major pathway, where veterinary pharmaceuticals contaminate soil and water systems *via* animal waste. According to the MEC database (Fig. 11 in ref. 24), in Africa, a large share of reported emissions originates from animal farming, with smaller contributions from urban and other sources. In Asia, emissions are distributed across several categories, with notable shares from animal farming, urban sources, and industrial applications. In Latin America and the Caribbean, entries show relatively higher proportions from urban environments and manure/sludge, while in Eastern Europe, contributions are mainly from urban and manure/sludge sources, together with hospital wastewater. In Western Europe and Other Group, the database likewise indicates a predominance of urban and manure/sludge emissions, with smaller inputs from hospital wastewater and other identified categories.

3.2. Impact of different sources on contamination levels and exposure

The impact of various pharmaceutical sources on environmental contamination and exposure is shaped by multiple factors. These include the nature, amount, and release frequency of the pharmaceuticals, along with the environmental conditions and the dynamics of how these substances are transported and transformed.[25]

The pathway of these contaminants from their source to the environment involves several steps, including transport through sewage systems, leaching into groundwater, and runoff into surface waters (Fig. 2). Typically, the contamination levels and exposure are higher near the point sources, such as manufacturing plants and hospitals, than the diffuse sources, such as settlements and agricultural settings. However, the diffuse sources can also contribute to the accumulation and persistence of pharmaceuticals in the environment over time.[26]

The migration of these contaminants involves various processes, primarily surface runoff, soil leaching, which represent the dominant aqueous pathways.[26,27] While volatilisation and subsequent atmospheric deposition are also potential transport routes, they are generally considered minor pathways for the vast majority of active pharmaceutical ingredients (APIs). This is because most APIs have low volatility, as characterised by experimentally and theoretically determined Henry's Law constants.[28] Additionally, environmental factors, such as temperature, pH, oxygen levels, organic matter and the presence of living organisms, play a role in shaping the behaviour and impact of these contaminants in natural settings.[25,27]

3.3. Impact of regulatory policies on contaminant sources

Regulatory policies play a crucial role in controlling and reducing the sources of pharmaceuticals in the environment. However, the current global regulatory framework is fragmented and inconsistent across different countries and regions.[15] Presently, there is no universal standard or agreement for the assessment and management of pharmaceuticals in the environment. Most of the existing regulations are primarily focused on the quality, safety, and efficacy of pharmaceuticals for human and animal use, rather than their environmental impact. Some regions, such as the European Union (EU), have taken more cautionary approaches to regulating pharmaceuticals in the environment. The EU requires environmental risk assessment (ERA) for new pharmaceuticals, endorses the principle of green pharmaceuticals, and promotes the proper disposal and take-back of unused medicines.[29] However, these measures are still limited and insufficient to address the variability in enforcement, regulation, and monitoring efforts aimed at alleviating environmental risks. In contrast, other countries, such as the United States (US) and Canada, have less stringent and comprehensive regulations for pharmaceuticals in the environment. In the US, multiple agencies address environmental pollution in their sectors. Moreover, in various regions across Canada, there are no formal policies or regulations in place that specifically govern pharmaceuticals and personal care products.[15]

Wilkinson *et al.* (2022) provide a comprehensive assessment of API pollution in rivers across 104 countries, analysing samples from 1052 sites and identifying 61 different APIs. This global dataset underscores significant geographic variations in

Table 1 Region-level pharmaceutical exposure metrics derived from Wilkinson *et al.* (2022)

Region/Economic classification	Mean cumulative API concentration (μg L^{-1})	Typical range for single APIs (ng L^{-1})
South America	10.66	21.9–7832.0
Asia	10.10	16.6–6725.0
Africa	9.49	20.8–9476.0
North America	3.66	12.4–1764.0
Europe	2.55	15.2–1618.0
Antarctica	0.97	68.2–1072.8
Oceania	0.22	17.8–489.7

pharmaceutical contamination levels, with the highest concentrations detected in regions with less stringent regulatory frameworks and inadequate waste management infrastructure.[12] The study highlights that the highest cumulative API concentrations are found in sub-Saharan Africa, South Asia, and South America areas (Table 1), typically characterised by limited regulatory oversight and poor wastewater treatment facilities. In contrast, regions with more robust regulatory policies and advanced waste management systems, such as Europe and North America, generally show lower API concentrations. For instance, European Union (EU) countries, which mandate environmental risk assessments (ERAs) for new pharmaceuticals and promote proper disposal and take-back schemes, exhibit relatively lower contamination levels.[12] To effectively manage pharmaceuticals in the environment, there is a need for more harmonised and effective regulatory policies at the global, regional, and national levels. This also calls for the active engagement and cooperation of diverse stakeholders, including the pharmaceutical industry, the healthcare sector, environmental bodies, the scientific community, and the public. It is notable that the European Commission is currently revising legislation around pharmaceuticals as part of their Pharmaceuticals Strategy for Europe, offering the potential for strengthened environmental protection,[30,31] harmonised at the regional level.

As regulation develops to meet these challenges, it is crucial that the tools used to enforce it keep pace. Fate and exposure models are a key method by which industry and regulators can perform prospective risk assessments, for example, by using them to predict environmental concentrations of pharmaceuticals based on hypothetical use volumes and emissions.

4 Overview of fate and exposure modelling: historical perspective

Environmental fate models provide a quantitative and mechanistic way to understand how chemicals move, transform, and accumulate in the environment. Combined with multi-pathway exposure models, they estimate how organisms are exposed to chemicals and how humans are exposed *via* the environment, including through human food and water sources and dermal contact. The development of these models has advanced significantly by focusing on specific areas for improvement, such as establishing clear chemical classification systems, enhancing the algorithms used in the models, and conducting thorough sensitivity analyses.[32]

The advancement of environmental fate and exposure modelling has been propelled by collaborative initiatives among model creators and users, primarily through workshops and working groups. In 1994, two pivotal workshops were organised by the Society of Environmental Toxicology and Chemistry (SETAC) in Leuven, Belgium, and Denver, Colorado. These events convened 30 model developers and users to deliberate on the application of environmental fate and exposure models, assess their efficacy, offer guidance on their utilisation, and suggest enhancements. These dialogues established a foundation for wider acceptance and promoted the adoption of these models.[32]

Fast forward to October 2001, seven years later, a workshop was held in Ottawa, Canada, under the joint organisation of OECD/UNEP. The focus of this workshop was on the effectiveness of multimedia fate models in estimating the overall environmental persistence and long-range transport of chemicals, especially persistent organic pollutants (POPs) and substances that are persistent, bioaccumulative, and toxic (PBTs). The outcomes of this workshop included a published comparative study of models, recommendations for using models to evaluate persistence and long-range transport, and the creation of the OECD Overall Persistence and Long-range Transport Modeling Tool[32,33]

In 2013, a working group, jointly organised by the scientific committees of the European Commission (SCHER, SCHENIR, SCCS), released a scientific opinion titled "Addressing the New Challenges for Risk Assessment". This document highlighted opportunities to refine exposure models to enhance their ecological realism and predictive capacity for an expanding array of chemical classes, including engineered nanomaterials (ENMs). The transition from theoretical usage to practical implementation in scientific and policy contexts signifies the evolution of these models into dependable tools.[32]

One notable advancement in this field has been the modelling of ENMs, which have different behaviour and environmental impacts from their bulk forms and from substances which more readily dissolve in water. Conventional equilibrium partitioning models, which have been the cornerstone of exposure modelling, are less applicable to ENMs due to the ability of particulates like nanoparticles to form thermodynamically unstable suspensions.[34] The application of fate models to ENMs shows the need to adapt existing models to new classes of contaminants, a challenge also relevant to pharmaceuticals. In the case of ENMs, conventional exposure models were updated to include nano-specific processes such as heteroaggregation to suspended matter, attachment to solid matrices, size-dependent dissolution, biofouling and incorporating updated emission data.[8,32,34] These updates laid the foundations for modelling other particulates such as microplastics, which, similarly to ENMs, require specific process descriptions such as fragmentation and additive release.[35–38]

Work on engineered nanomaterials and microplastics has served as a methodological analogue for situations in which

classical equilibrium-partitioning assumptions break down.[34–38] Historically, these efforts prompted the introduction of non-equilibrium transport, size- and surface-mediated interactions, and explicit aggregation to environmental particles and dissolved organic matter. Similar departures are germane to pharmaceuticals: robust exposure assessment often requires pH-dependent speciation, light and DOM modulated transformation, and, critically, explicit representation of transformation products.[39–41] Framed in this way, the ENM/microplastics experience clarifies why model choice and parameterisation for pharmaceuticals must diverge from those for neutral, persistent organics and points toward the process modules emphasised in subsequent sections.[10,42–44]

Distinct challenges remain in modelling pharmaceuticals, and their unique and varying physicochemical properties, like ENMs, motivate the development of bespoke fate and exposure models. For example, conventional chemical exposure models often rely on partition coefficients such as the octanol–water partition coefficient (K_{OW}) that might not fully account for the behaviour of polar (ionisable) compounds, which comprise around 80% of orally ingested pharmaceuticals.[45] Additionally, the bioavailability of pharmaceutical compounds can be significantly modified by the chemistry of the environment they are in, and they can degrade into myriad transformation products, which may have similar or even elevated hazard profiles compared to the original compound. Conventional exposure models commonly treat transformation (a form of breakdown, including degradation) as a loss process, which will lead to underestimates of risk for compounds with hazardous transformation products. Fully understanding the impact of pharmaceuticals on environmental and human health requires a multidimensional approach that takes into account all of these factors.

5 Models predicting pharmaceutical fate and exposure in the environment

This section examines and compares commonly used models for local, regional, and global pharmaceutical fate and exposure modelling. It includes both standalone and web-based models, such as QWASI, SimpleBox, GREAT-ER, PhATE, Global-FATE, ePiE, iSTREEM, WASP, QUAL-2E and QUAL-2K, AQUASIM, USEtox, PERK, GWAVA, ChimERA, SESAMe and MAMI. Most of the selected models have not been developed explicitly to analyse the fate and exposure of pharmaceuticals but have been implemented for pharmaceutical case studies. The review focuses on their environmental applicability, sources simulated, and other aspects to provide a comprehensive understanding of each model's capabilities and limitations (SI Table 1).

Mathematical simulations for pharmaceuticals in environmental systems have improved by incorporating various physico-biochemical, hydrological, and hydrodynamic interactions.[43] A key component of these models is the precise representation of mixing during transport in rivers. The type and direction of mixing depend on the specific needs and characteristics of the simulation and can be shown through fugacity (multimedia box) modelling, one-dimensional (1D) watershed modelling, two-dimensional (2D) and three-dimensional (3D) hydrodynamic modelling.[9] Fig. 3 represents the major paths of modelling pharmaceuticals in the environment.

1D models are often used in rivers with little human interference, where longitudinal dispersion is the main mechanism under natural flow conditions. However, in rivers with major human alterations, such as dams or canals, and in still waters, mixing is affected by several factors, such as hydrodynamics, secondary flow, and aquatic life. In these situations, the modelling becomes more complex, and 2D or 3D models are more suitable to realistically depict mixing dynamics.[9,46] On the other hand, 2D/3D water quality models offer a more complete picture of pharmaceutical fate, interactions, and transport within water bodies. These models can be classified by gridded approaches or segmentation of river networks, each with different data needs and computational efficiency. Moreover, probabilistic simulations are used to account for temporal variability in concentration due to discharge changes.[9]

1D models help evaluate runoff and pollutant loadings at the catchment scale, concentrating on physical transport processes. However, they may not be able to simulate interactions across multiple environmental compartments, which can be

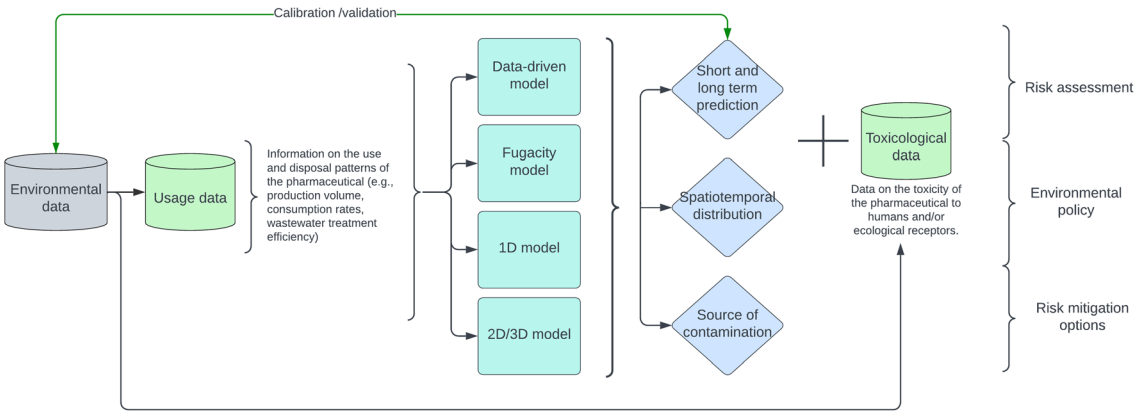

Fig. 3 Flowchart of the pharmaceutical modelling framework and prospective applications.

addressed by linking them with fugacity models. Fugacity models are good at simulating the behaviour of pharmaceuticals across different environmental media (air, soil, water, and sediment), but make the modelling process and data requirements more complicated.[9,47]

Model coupling, which integrates, for example, external hydrological, hydrodynamic, and emission models, is a common and effective practice in pharmaceutical transport simulation. However, simulations also depend on in-stream reaction kinetics, which are challenging to quantify due to the dynamic and complex nature of transport processes. Hybrid modelling frameworks, which combine laboratory kinetic results with numerical modelling, can improve the understanding and prediction of the persistence and removal of pharmaceutical compounds in the environment.[9,48,49] These predictions are crucial for risk characterisation and exposure assessment, which require selecting a suitable fate model based on several factors such as spatial resolution, emission, fate estimation mechanisms, and specific parameters such as polarity and degradation mechanisms. The accuracy and reliability of these models can be further enhanced by incorporating real data input from field measurements and monitoring.

5.1 Fugacity models

Fugacity was originally proposed as a concept in chemical thermodynamics by Gilbert Lewis in the early 20th century[50] as a method for calculating chemical equilibrium partitioning. It was later revised by Donald Mackay, who established the basis of the fugacity model.[51] It is a widely used tool for multimedia fate modelling, for example, being used in SimpleBox, the regional-scale fate model underpinning the EU regulatory tool EUSES (EU System for the Evaluation of Substances), and the OECD Overall Persistence and Long-range Transport Potential tool.[33,51] Fugacity models allow for the estimation of the chemical transport, concentrations, and exposure in different environmental media, such as air, soil, water, biota, suspended solids in water, and sediment. Multimedia fugacity models usually treat the environment as large, spatially averaged boxes with rate constants or fugacities used to partition chemicals between these boxes.

Fugacity models can handle both steady-state and dynamic scenarios and have four levels of complexity. Level I assumes that all media are at equilibrium with a constant amount of chemicals, while Level II accepts that there is a constant input of chemicals into all media. Level III accounts for a non-equilibrium situation with constant input,[52,53] whereas level IV deals with a dynamic situation where input rates, concentrations, and fugacities change over time.[54]

The models predict the concentrations, distributions, persistence, fate, and transfer patterns of chemicals in specific regions, based on the relationships among fugacity, fugacity capacity, concentration, and various transfer coefficients. They have been enhanced over time to incorporate more media, such as vegetation, to include non-diffusive processes, such as wet deposition,[50,51,55] and to cope with substances like ENMs for which equilibrium partitioning yields inaccurate predictions.[34,56]

Several studies have applied fugacity models to examine the environmental fate of pharmaceuticals. Żukowska *et al.*[53] demonstrate the applicability of multimedia models by employing a level III fugacity model based on poly-parameter linear free energy relationships (pp-LFERs). This study estimates the mass balance of chemicals in air, water, soil, and sediment. The model assumes equilibrium within each medium, but not between them. It considers diffusion, advection, and degradation processes in all media. The model inputs are environmental characteristics, physical–chemical properties, half-lives, and emission rates of the chemicals. The model outputs are concentrations, transport rates, advective flow, degradation rates, and persistence of the chemicals in the media. Additionally, Chen *et al.*[54] developed a dynamic level IV fugacity model to investigate the fate of antibiotics in Beijing, a metropolis with water scarcity. The dynamic model accounts for four media (air, water, sediment, and soil) and includes antibiotic emissions from human and animal sources, air/water flow, intermedia transfer, degradation, and wastewater irrigation from water to soil. The model accurately reproduced the observed concentration data and revealed the risks of antibiotics in the aquatic environment. Meanwhile, Trapp *et al.*[57] proposed an activity-based concept for the transport and partitioning of ionising organics. Activity-based approaches have long been central to geochemical speciation models such as MINTEQA2,[58] PHREEQC,[59] and WHAM,[60] which can handle both inorganic ions (*e.g.* metals) and ionizable organic acids (*e.g.*, citric and lactic acids). However, the concept of "activity capacity" introduced by Trapp *et al*. represents a more recent development specific to multimedia environmental fate modelling. The concept suggests a system of equations based on activity similar to the fugacity approach. The study demonstrated the influence of pH on concentration ratios for pharmaceuticals in a multimedia lake system.[57]

Inspired by the fugacity approach, researchers have created various other models to suit different systems. Some of the notable models are the Quantitative Water, Air, and Sediment Interaction (QWASI) model and SimpleBox, which we detail further below.

5.1.1 QWASI. QWASI is a multimedia fate fugacity model that estimates the concentration of pharmaceuticals and other organic pollutants in air, sediment, and water. It is based on mass conservation, with mass balance equations for each environmental phase.[51] It is mainly used to simulate pollutants in lakes, assuming a uniform level of water mixing.[61] Contaminants are removed from the lake by evaporation, reaction in water and sediment, water outflow, and sediment burial. Therefore, the model needs various parameters depending on the simulation level: geographical and physical parameters (*e.g.*, lake area, sediment depth, suspended solid concentration and density, sediment burial, sedimentation, resuspension, mass transfer coefficient, organic carbon fraction in sediment and water, sediment oxygen demand, inflow concentration and discharge), water quality (*e.g.*, temperature, salinity) and contaminant properties (*e.g.*, water solubility, $\log K_{OW}$,

hydrolysis, photolysis, volatilization, melting point).[62] The mass balance equations for the well-mixed water and sediment also include sediment-water exchange by diffusion, deposition, and resuspension.[61,62] QWASI can also study environmental changes due to temporary or permanent changes in environmental properties.

5.1.2 SimpleBox. The SimpleBox model, a key component of the European Union System for the Evaluation of Substances (EUSES), is a multimedia fate model designed to simulate the environmental fate of chemicals across air, water, sediment, and soil compartments at regional, continental, and global scales.[63,64] Developed initially in the 1980s, SimpleBox has undergone multiple revisions, with significant updates in version 4.0 [65] and more recent updates to include particulate matter such as nanomaterials[56] and microplastics.[37]

Unlike earlier fugacity-based models, SimpleBox calculates chemical mass flows and concentrations using concentration-based "piston velocity" coefficients, which better account for transport between compartments.[66] The model uses mass balance equations, internally solving for fluxes based on physical and chemical properties and user-specified emission rates to generate predicted environmental concentrations (PECs).

One of SimpleBox's major strengths is its flexibility in compartmentalisation, allowing simulations at various scales through a nested local-regional-continental structure and an ability to adjust environmental compartments like air, freshwater, soil, and sediment. Over the years, the model has seen several enhancements, such as the incorporation of temperature-dependent chemical properties, the addition of deep ocean compartments, and the removal of the local scale and vegetation compartments to improve simplicity.[65]

SimpleBox is particularly noted for its role as the regional distribution module in EUSES and is integrated into tools like Chesar for chemical safety assessments under the REACH regulation.[67] It provides an effective screening-level tool for environmental fate assessments, predicting steady-state concentrations across various compartments while balancing complexity and usability.

Recent studies highlight SimpleBox's applicability in environmental fate studies, especially for neutral substances, organic acids, and metals. Nonetheless, its conservative approach makes it a valuable first-tier model for chemical risk assessments across broader regions. However, it remains limited in addressing temporal and spatial variations and may overpredict PECs compared to measured environmental concentrations.[68]

5.2 Spatial models

5.2.1 GREAT-ER. The GREAT-ER (Geography-referenced Regional Exposure Assessment Tool for European Rivers) is a catchment-scale model for understanding the fate and impact of various chemicals, particularly pharmaceuticals, in river basins.[10,69] It uses both deterministic and stochastic (Monte Carlo simulation) methods to estimate the aquatic exposure of various contaminants. Moreover, it integrates Geographic Information Systems (GIS) and chemical models to simulate chemical behaviour at the river basin level. It includes parameters such as physicochemical properties, hydrological data, consumption patterns, and removal efficiencies.[69–71]

One of the GREAT-ER model's core elements is its ability to calculate emissions from different sources and their distribution along river segments. This emission calculation considers factors such as population data, consumption data, water usage, and wastewater treatment plant (WWTP) efficiencies.[71] It takes into account the hydrological dynamics of river systems, including flow measurements. The model divides rivers into segments and calculates the flow, velocity, and loadings for each, including contributions from tributaries and WWTPs.[70,71]

Using Monte Carlo simulations in the GREAT-ER model enables the handling of variabilities and uncertainties in parameters like flow rates, emission rates, and WWTP removal efficiencies.[70] This stochastic approach is beneficial for understanding the temporal variation in the concentrations of pharmaceuticals and other chemicals. The model also supports the evaluation of potential risk management scenarios and the impact of regulatory measures on water quality.[10,72]

Several studies demonstrate the adaptability and effectiveness of GREAT-ER in predicting pharmaceutical exposures. For instance, Aldekoa *et al.*[73] applied it to model diclofenac, a non-steroidal anti-inflammatory drug, in the Llobregat River Basin in Spain, while Kehrein *et al.*[10] applied an improved version of GREAT-ER to model diclofenac in the Ruhr River, highlighting the model's capability in realistic prediction and management scenario evaluation. GREAT-ER has been improved to have better analysis tools, faster Monte Carlo simulations, and new functionalities for scenario creation and analysis. In a study by Alder *et al.*[74] GREAT-ER was used to predict the concentrations of β-blockers in the Glatt Valley Watershed, Switzerland. The model's predictions were within a factor of two of measurements, demonstrating its accuracy in estimating average daily concentrations in rivers.

A detailed analysis was done by Hannah *et al.*[75] using GREAT-ER to evaluate concentrations of 17a-ethinylestradiol in US and European waters. Their results showed that most measured concentrations were low and aligned with the model's predictions, suggesting these levels could be used for conservative risk assessments. On the other hand, a more specific analysis was explored in the study of Robinson *et al.*.[76] They applied GREAT-ER to assess the impact of photo transformation on the degradation of propranolol hydrochloride in rivers. The study found that this process considerably reduced the environmental concentrations of the drug, especially in clear, slow-flowing rivers during summer.

Additionally, in the context of antibacterial and antifungal agents, Capdevielle *et al.*[48] used GREAT-ER to analyse the presence of triclosan in freshwater environments. This study emphasised the model's ability to validate simulated concentrations with real-world monitoring data, offering insights into the potential risks of chemicals like triclosan under various environmental conditions. Monte Carlo simulation is used to incorporate probability density functions for key inputs like WWTP removal and river flow, providing probability distributions for river chemical concentrations. Moreover, Archundia

et al.[77] used it to assess the environmental fate and ecotoxicological risk of sulfamethoxazole in the Katari catchment of the Bolivian Altiplano. Unlike Capdeivielle *et al.*, this study was performed deterministically, focusing on pharmaceutical emissions from discharge points and river segments. Emissions are calculated using local population data, water, and pharmaceutical consumption rates. They also incorporated a risk analysis tool for calculating Predicted Environmental Concentration/Predicted No Effect Concentration (PEC/PNEC) ratios.

Lammchen *et al.*[49] demonstrated the utility of GREAT-ER in conjunction with targeted monitoring for assessing pharmaceutical concentrations in German watersheds. Their approach highlighted the model's proficiency in predicting a range of spatial surface water concentrations and evaluating the impact of local pharmaceutical emissions. GREAT-ER employs mass balance equations to monitor chemical emissions into surface water, accounting for their removal in wastewater treatment plants. The model incorporates pseudo-first-order processes such as sedimentation, volatilisation, and degradation (*via* photolysis, hydrolysis, or biological means) for in-stream loss, and follows mass conservation principles where each river segment's input equals its output, modified by diffuse emissions or loss processes. The river system is depicted as a detailed hydrological geometric network divided into segments up to 2000 meters long, with nodes at confluences, emission points, and sites of interest. Point source emissions, primarily from wastewater treatment plants, are estimated using submodules, discharged at respective nodes, and then transported downstream, with emission loads expressed as mass per unit time under steady-state conditions. Additionally, Duarte *et al.*[72] employed GREAT-ER to define ecological risk profiles for various pharmaceuticals in the Vecht River, illustrating the model's role in transboundary river basin assessments.

The model features two hydrological scenarios: low-flow (typical of dry summer periods) and average flow, where physicochemical loss processes like (bio)degradation and photolysis are considered, excluding hydrolysis and volatilisation due to their minimal impact on pharmaceuticals.

In summary, the GREAT-ER model stands as a robust tool for predicting and managing the fate of chemicals in surface water. It allows for the assessment of environmental concentrations, facilitating risk management scenarios and potential regulatory impacts on water quality. Its application across numerous studies underscores its adaptability and effectiveness in addressing the environmental challenges posed by pharmaceuticals and other chemical contaminants. Table 2 summarises studies from the literature that apply the GREAT-ER model to estimate concentrations of down-the-drain contaminants.

5.2.2 PhaTE. The fate of pharmaceuticals from point sources in aquatic environments can be simulated by the deterministic Pharmaceutical Assessment and Transport Evaluation (PhATE) model. This model divides rivers into distinct segments and uses a mass balance equation for each segment to monitor the fate of contaminants.[43] A key feature of this model is that it accounts for pollutant loads from both upstream and WWTPs (if any) in each river segment, as well as first-order in-stream decay, abstractions, and flow to the next segments.[43]

PhATE models river segments as plug-flow reactors and reservoirs as well-mixed tanks. This means that reservoirs are seen as a series of tanks, with mass concentration moving from one tank to another due to advection. The mass load from WWTPs is calculated by multiplying the average annual compound per capita consumption by the population served and adjusting for loss factors from human metabolism and WWTP removal efficiency.[43,70,71] All relevant in-stream transport processes are then added to a total first-order loss rate constant, with the PhATE model using Microsoft Visual Access database and GIS for data management and watershed hydrologic data.[43] The main uses of PhATE are in exposure assessment, estimating PECs of pharmaceuticals in surface waters, and in risk assessment, estimating PNECs. The model's emphasis on WWTPs as the main source of pollutants in catchments requires extensive input data, such as compound use and characteristics, and detailed catchment characterisation. This data-intensive approach, while ensuring accuracy, also poses difficulties in setting parameters for emerging contaminants.[43,70,71]

The model was introduced by Anderson *et al.*[43] as a tool for estimating concentrations of pharmaceuticals in U.S. surface waters due to patient medicine consumption, using a mass balance approach in 11 representative watersheds. PhATE's capabilities extend beyond just surface water simulation; it can also estimate concentrations of pharmaceuticals in biosolids and sludge from WWTPs. This breadth of application was exemplified in many studies. Hosseini *et al.*[78] further demonstrated the model's usefulness in applying PhATE to the Canadian climate to simulate concentrations of various pharmaceuticals and personal care products in the Grand River watershed. The model was calibrated using seasonal hydrological parameters and chemical loss parameters. It proved to be effective in simulating pharmaceuticals with continuous human use, with validation indicating reliable concentration simulations, especially for persistent substances like carbamazepine. A specific study on patient consumption of antibiotics in the United States surface waters was done by using PhATE.[79] The findings suggest that various antibiotics with different modes of action and physical–chemical properties may be present in environmental compartments at or above the levels considered safe to prevent antimicrobial resistance spread.

Some studies effectively utilised both the PhATE (Pharmaceutical Assessment and Transport Evaluation) and GREAT-ER (Geography-referenced Regional Exposure Assessment Tool for European Rivers) models to assess the environmental concentrations of various pharmaceuticals and personal care products in surface waters. In a study by Hannah *et al.*,[75] the concentrations of 17a-ethinylestradiol in surface waters of the United States and Europe are examined. Both PhATE and GREAT-ER models were used to generate PECs in these regions. The results showed that most measured environmental concentrations (MECs) matched the models' predictions, providing insight into conservative estimates for risk assessment purposes. Similarly, in the research that focused on triclosan

Table 2 Reviewed studies using the REAT-ER model

Reference	Study environment	Contaminant modelled	Method
64	Llobregat River in Catalonia in Spain	Diclofenac	The deterministic approach is applied to specific campaign data The stochastic method considers the variability in daily water flow and velocity over a range of years
60	The watershed of the Ruhr River in Germany	Diclofenac	Simulation inputs, including consumption, excretion, and photolysis rates, were assigned probability distributions based on the literature
66	Watersheds in Germany, Italy, the United Kingdom	17a-Ethinyl estradiol	Concentration data from the literature The model performs simple mass balance calculations using the GREAT-ER model
67	The Aire–Calder catchment in the United Kingdom	Propranolol hydrochloride	The stochastic method used to analyse the mean and percentile concentrations downstream Distinct degradation processes, photo transformation, in the removal of pharmaceuticals in rivers
65	The Glatt Valley Watershed in Switzerland	β-blockers	Flow conditions, velocities, and residence times in the watershed were modelled using data from 16 gauging stations, with lakes represented as mixed boxes
		Atenolol Sotalol Metoprolol Propranolol	Deterministic simulations were applied to reflect specific flow conditions during the sampling period
48	The Aire–Calder catchment in the United Kingdom	Triclosan (TCS)	Model predictions were based on assumptions like triclosan usage and varied WWTP removal rates
68	Katari catchment of the Bolivian Altiplano	Sulfamethoxazole	The model calculates emissions from specific river segments and WWTPs, factoring in population, water, and drug use It includes a risk assessment using the PEC/PNEC ratio
39	German watersheds	Clarithromycin	Mass balance equations, considering removal processes in WWTP
		Iopamidol	River network as a series of interconnected segments and nodes
		Ethinylestradiol (EE2)	Emission loads are calculated and treated as constant over time for each segment
63	Vecht River in Netherland	Carbamazepine ciprofloxacin	The model integrates a hydrological network, an emission model, and a fate model
		17a-Cyclophosphamide diclofenac Erythromycin Ethinylestradiol Metformin	The model operates two hydrological scenarios: low-flow and average-flow
		Metoprolol	Physicochemical loss processes like (bio)degradation, sedimentation, and photolysis

(TCS), a common antimicrobial agent, both PhATE and GREAT-ER models are used to predict in-stream concentrations in European and US surface waters.[48] In another study, Robinson and colleagues used both models to investigate the effect of direct photo transformation on the environmental concentrations of propranolol hydrochloride.[76] This study showed that

incorporating photo transformation kinetics into the PhATE and GREAT-ER models notably changed the predicted environmental concentrations, depending on different seasonal and river conditions. It is important to note that in the GREAT-ER model, photo transformation is treated as a first-order loss process, focusing primarily on the photodegradation rate of chemicals without tracking the transformation products. This simplification might limit the model's ability to predict complex behaviours of transformation products in the environment. On the other hand, the PhATE model uses a single overall first-order degradation rate constant, representing a sum of all contributing degradation processes, without differentiating among specific mechanisms such as photo transformation.

PhATE's effectiveness is demonstrated by its ability to estimate environmental concentrations in surface waters under different stream flows and WWTP inputs, as well as wastewater plant biosolids. The model's usefulness is especially evident when analytical methods fail to detect compounds in the field, allowing for potential environmental risk assessments through PEC and PNEC comparisons. The PhATE model, thus, serves as an important tool in the environmental assessment of pharmaceutical pollutants, offering a detailed and accurate picture of their fate in aquatic systems. Table 3 summarises studies from the literature that use the PhATE model.

5.2.3 GLOBAL-FATE. GLOBAL-FATE is a GIS-based model designed to simulate the fate of human pharmaceutical and chemical compounds in the global river network, including lakes and reservoirs. This model is most suitable for solving the steady-state concentrations of contaminants originating from point sources, particularly those discharged down to the drain into various aquatic environments like small streams, rivers, lakes, and reservoirs.[44]

Table 3 Reviewed studies with PhATE model

Reference	Study environment	Contaminant modelled	Method
34	11 catchments in the USA	Triclosan	-The model uses a mass balance approach to estimate pharmaceutical concentrations
		11 APIs	It accounts for pharmaceutical inputs from upstream sources and losses through in-stream processes
69	Grand river catchment in Canada	Ibuprofen	The model uses a mass balance approach to estimate pharmaceutical concentration
		Naproxen carbamazepine Gemfibrozil	It combines literature-derived parameters with seasonal hydrological data for calibrated
70	Columbia and Sacramento watersheds in the USA	11 most sold antibiotics	The model divides rivers into discrete segments. It estimates the mass of pharmaceuticals that enter a segment from upstream or from the wastewater treatment plant (WWTP)
66	11 catchments in the USA	17a-ethinyl estradiol	Concentration data from the literature
			The model performs simple mass balance calculations and utilises the PhATE model
48	11 catchments in the USA	Triclosan (TCS)	The model estimated river water exposure, using data from 11 diverse catchments and considering over 1100 WWTPs as pollution sources
			In this study, the PECs derived from the PhATE and GREAT-ER models were compared to PNEC from species sensitivity distribution
67	The Mississippi	Propranolol hydrochloride	The model calculates chemical removal in STPs, rivers, and drinking water treatment using a comprehensive first-order degradation rate constant
	Headwaters and the lower		It differs from the GREAT-ER model by not separating degradation mechanisms into individual sub-models
	Colorado river catchments in the USA		

A key feature of GLOBAL-FATE is its ability to account for multiple concentration mechanisms for human medicines. These include loss from human metabolism, removal by wastewater treatment plants (WWTPs), dilution, and first-order mass decay. The model computes contaminant loads based on population data and per capita consumption and converts this into the mass load of contaminants reaching the river network. The model integrates geographical and hydrological data, covering the shape, location, and volume of lakes and reservoirs, with contaminant datasets. Input load is either directly introduced into the river system or adjusted based on the removal efficiency of WWTPs. GLOBAL-FATE uses basic GIS modules to compute routing, including flow accumulation and direction in each river reach or raster cell. The model applies attenuation mechanisms sequentially along the river reach to obtain the final concentration of contaminants.[44]

GLOBAL-FATE is adaptable, written in C, and can be run on any platform, using inputs in standard GIS formats. It can also be run as a plug-in for the Quantum Geographic Information System (QGIS). GLOBAL-FATE can evaluate the effectiveness of large-scale management strategies, such as pharmaceutical consumption control and the implementation or upgrading of wastewater treatment, highlighting its potential impact on environmental policy and sustainable management of aquatic ecosystems.

5.2.4 ePiE. The ePiE (exposure to Pharmaceuticals in the Environment) model is a novel approach to environmental risk assessment, designed to calculate the concentrations of pharmaceuticals in European surface waters with high spatial resolution (~1 km), while requiring limited computational resources and data. The ePiE model divides the river system into a series of compartments, each connected by nodes that represent emission points, river junctions, and the inlets and outlets of reservoirs and lakes.[42]

A key feature of ePiE's functionality is the FLO1K GIS-based dataset, which provides essential hydrological information. It also uses various databases like HydroSHEDS, HydroLAKES, UWWTD-Water, and Hydro-BASINS to accurately represent nodes, lakes, WWTPs, and basins. This model incorporates more than just hydrological data, adding gridded information on climate (such as air temperature and wind speed), hydrology, and geochemical aspects (like soil and slope characteristics, and chemical properties) for each node in the river network.[42] Emissions to these nodes are calculated using consumption data and population metrics, accounting for reductions due to human metabolism and the removal efficiency of WWTPs. The model applies dilution and loss mechanisms in surface waters based on mass balance equations along the nodes. For lakes and reservoirs, ePiE treats them as single, well-mixed tanks, considering additional parameters like hydraulic retention time and volume.

Oldenkamp *et al.*[42] developed ePiE to balance the need for high spatial resolution data with manageable computational and data requirements. Its effectiveness was shown through a comparison with measured concentrations of 35 APIs in the river Ouse (UK) and Rhine basins (Northwest Europe). The result of the study showed a high degree of accuracy, with around 95% of predictions within an order of magnitude of actual measurements. Especially in the river Ouse basin, the model achieved even more accurate predictions due to the availability of reliable consumption data and a monitoring study design that matched the model outputs. Austin *et al.*[80] further explored the utility of ePiE in assessing ibuprofen exposure across Europe. This study highlighted the model's value as a cost-effective alternative to extensive environmental monitoring. It validated the ePiE model with the most accurate available consumption data. Moreover, it showed its effectiveness in making exposure predictions for ibuprofen by comparing the model predictions with measured river concentrations. The study emphasised the importance of incorporating specific regional information, such as customised WWTP removal rates, to improve the model's realism and accuracy.

In summary, the ePiE model is a powerful tool in the environmental risk assessment of pharmaceuticals, offering a large-scale, high-resolution approach to predict the concentrations of pharmaceuticals in surface waters. It can integrate diverse datasets, along with its proven accuracy in real-world applications.

5.2.5 iSTREEM. The iSTREEM model is designed to assess the fate of chemicals used in down-the-drain products. This web-based model (https://www.istreem.org/) is a vital tool for product stewardship and regulatory compliance, helping chemical suppliers and manufacturers across various commodity groups to understand the environmental impact of their products.[11]

iSTREEM is specially designed to estimate the concentration of trace contaminants, including antibiotics, in various parts of the water system. These parts include WWTP effluents, water supply intakes, and receiving water bodies, mainly across the continental United States, China, and Japan. The model gives conservative estimates of chemical concentrations under mean and low-flow conditions in streams and rivers, enabling risk assessments for these estimated concentrations.[11] The model builds on the foundations of earlier models like a river quality model ROUT and the GIS-based river water quality model (GIS-ROUT). ROUT describes WWTP loading, instream loss, and chemical properties, while GIS-ROUT integrates spatial data through a digitized river network, allowing comprehensive spatial data analysis. iSTREEM uses per-capita consumption data to calculate WWTP effluent concentrations and uses Visual Basic and ArcGIS to represent the river network and conduct unique analyses for each reach. The river reach in iSTREEM is segmented, with each segment accounting for upstream contributions, WWTP discharges, and losses due to instream degradation processes, including adsorption and biodegradation, which are the main decay processes.

The initial study by Kapo *et al.*[11] showed the model's utility in a broad-scale in-stream exposure assessment of down-the-drain chemicals, providing a publicly accessible way to estimate concentrations of such chemicals across national and regional scales. They showed how iSTREEM results could be used to derive a PEC by focusing on the high end of the concentration distribution. Moreover, Ferrer and DELeo[81] extended iSTREEM's scope by developing a single-medium contaminant

fate model for the lower St. Lawrence drainage basin in Southern Ontario, integrating Canadian geographic data into the existing framework. They compared the model's PECs with measured surface water concentrations of chemicals like triclosan and carbamazepine. They found a close match between the two, especially when considering both mean and low-flow scenarios.

In summary, iSTREEM can be used to understand the environmental exposure of chemicals specifically from down-the-drain consumer products. Its ability to generate accurate predictions of chemical concentrations in various water bodies under different flow conditions makes it a valuable resource for environmental risk assessment and management in multiple geographies.

5.2.6 WASP. The Water Quality Analysis Simulation Program (WASP), developed by the United States Environmental Protection Agency (USEPA) and first presented by Di Toro *et al.*,[82] is a widely used dynamic model created to simulate the fate and transport of constituents in surface waters. It offers a flexible compartmental approach for addressing one-, two-, or three-dimensional problems.[83]

WASP features a hydrodynamic module based on the continuity and kinematic wave equations, enabling it to model both steady and unsteady one-dimensional water flows. The water quality module encompasses a wide range of pollutants, including metals, organic chemicals, and sediments. Besides the simulation of antibiotics, WASP has been extensively used to simulate conventional pollutants (*e.g.*, nutrients, dissolved oxygen, sediment oxygen demand, eutrophication, algae, and bacterial contamination), toxic pollutants (*e.g.*, organic chemicals, metals, mercury, pathogens), and persistent compounds. This model simulates various processes, including advection, dispersion, point and diffuse mass loading, and boundary interchange, as well as transformation processes like volatilisation, hydrolysis, photolysis, and biodegradation. Each segment is assumed to be thoroughly mixed, necessitating segmentation methods similar to those used in models like PhATE and GREAT-ER.

WASP has been employed in various research areas, including the study of biochemical oxygen demand, dissolved oxygen dynamics, nutrients, eutrophication, bacterial contamination, and heavy metal contamination. Additionally, it has been utilised to model pharmaceutical contaminants, as demonstrated in the research by Arlos *et al*. on selected anti-androgens and pharmaceuticals.[46]

5.2.7 QUAL-2E and QUAL-2K. The Corps of Engineers Quality 2-Enhanced (QUAL-2E) and its updated version, Corps of Engineers Quality 2K (QUAL-2K), are hydrodynamic water quality models developed by the US Environmental Protection Agency and designed to simulate water quality parameters in river systems. QUAL-2E, a one-dimensional laterally averaged model, calculates water quality parameters, including traditional components and emerging contaminants like antibiotics, by solving the advection–dispersion equation based on mass balance concepts. It assumes the river channel is well-mixed vertically and laterally, with the river divided into evenly spaced segments for simulation on a diurnal time scale.[70]

QUAL-2K, an enhancement of QUAL-2E, introduces the capability to simulate additional water quality parameters and allows for the division of the river into unevenly spaced segments. This version improves the simulation of light extinction effects on pollutant attenuation and includes features such as pH, total inorganic carbon, and the effects of generic pathogens on antibiotic concentrations. In QUAL-2K, these parameters are used in equilibrium and mass balance equations to simulate water quality. Both models have been applied in various studies to assess the impacts of nutrient concentrations on algal blooms, dissolved oxygen levels, and the fate and transport of both traditional and emerging pollutants, demonstrating their utility in managing and predicting water quality in surface water bodies.[70]

5.2.8 AQUASIM. The AQUASIM model was developed by Eawag (the Swiss Federal Institute of Aquatic Science and Technology) to simulate the behaviour and degradation kinetics of emerging contaminants, including personal care products and pharmaceuticals, in aquatic environments such as rivers, lakes, and reservoirs.[84] AQUASIM solves equations related to the mass balance of pollutants, by employing the implicit gear integration method and analysing kinetic parameter estimation.[84] The model's framework divides the aquatic system into discrete compartments and facilitates the modelling of various processes, including uniform and differential mixing. It also considers the effects of biological factors like algal and biofilm growth.[84] With its ability to perform simulations, parameter estimations, and sensitivity analyses based on real-world data, AQUASIM has been instrumental in understanding the environmental fate of compounds like pharmaceuticals, highlighting photodegradation as a key elimination mechanism.

5.2.9 USEtox. The USEtox model, led by the United Nations Environment Programme (UNEP) and the Society for Environmental Toxicology and Chemistry (SETAC), provides a complete tool for assessing human and freshwater impacts due to chemical emissions in life cycle assessments.[85] This model has been meticulously designed through a comparative analysis of existing toxicity characterisation models to provide robust and reliable characterisation factors (CFs) for toxicity impact assessment. These CFs are crucial as they quantify the potential impacts of chemical emissions, enabling assessments of both human toxicity and freshwater ecotoxicity.[85,86]

Characterisation factors within USEtox effectively integrate key components—environmental fate, human and ecological exposure, and toxic effects. This integration is vital as it allows the model to provide a comprehensive measure of a chemical's potential harm. The model is distinguished by its inclusion of significant model elements, such as the accounting for intermittent rain events and the nested configuration of urban within continental environments, which are critical for accurate impact assessment.[85]

USEtox provides a tool to stakeholders involved in life cycle impact assessment and environmental policy to model the distribution, degradation, and intrinsic damage of the substances.[85–87]

In addition to this, despite such large use and various types of substances in the database, coverage of pharmaceuticals by

the model is rather scant, underlining the blank spot for development. The USEtox structured approach in the determination of CFs that cover environmental fate, human and ecological exposure, and effects validates its appropriateness in pinpointing the ecological impact of pharmaceuticals and personal care products in aquatic environments and prioritising them for management and remediation efforts.

5.2.10 PERK. PERK is relatively unique in offering an interactive, web-based tool where the environmental risks of pharmaceuticals in surface waters can be analysed. It is an R-powered tool that calculates surface water PECs of a broad spectrum of pharmaceuticals, based on prescription data and wastewater treatment partitioning to predict emissions. Developed to align with standards from both the European Agency for the Evaluation of Medicinal Products and the United States Food and Drug Administration, PERK ensures robust methodology that meets international regulatory expectations.[88] While it has been implemented using prescription data in England, it should be noted that PERK primarily facilitates the comparison of predicted *versus* measured concentrations through its user-friendly dashboard, rather than offering geographical mapping of environmental footprints.[88] Its strength is in simplifying complex data and analysis into presentable, policy-relevant outputs, making it a useful tool in assessing the environmental impact of pharmaceuticals.

5.2.11 GWAVA. The Global Water Availability Assessment (GWAVA) model is a hydrological modelling tool that merges comprehensive datasets with local insights to predict alterations in water availability. It evaluates the effects of these changes on water quality and river ecosystems, making it an indispensable asset in the fields of environmental science and water management. Over the past twenty years, GWAVA has proven its versatility and resilience by being effectively applied at various scales, from continental to basin levels, in regions across Europe, Africa, and Asia.[89–91] GWAVA was used in a study that evaluated the potential concentrations of four antibiotics—ciprofloxacin (CIP), sulfamethoxazole (SUF), trimethoprim (TRI), and erythromycin (ERY)—in European rivers.[91] The research combined national antibiotic consumption data with excretion and sewage treatment removal rates to predict antibiotic concentrations in river water. The study constructed best, expected, and worst-case scenarios to estimate discharge levels and employed GWAVA, which uses a spatial resolution of approximately 6 × 9 km, to predict river concentrations based on 31 years of climate data.[91]

At its core, GWAVA employs a series of processes to simulate the interaction between environmental factors and human water systems. The model integrates a gridded Probability Distribution Model to emulate surface water and subsurface flow, incorporating natural water bodies such as lakes, wetlands, and glaciers, as well as human interventions like reservoirs and water transfers. It also addresses water demands from households, agriculture, livestock, and industries. GWAVA is engineered to function efficiently across spatial scales ranging from about 10 to 50 km (0.1° to 0.5° grid cells), offering the flexibility to operate on either monthly or daily time steps.[90,92]

GWAVA's global-scale methodology facilitates a consistent and in-depth exploration of water resource issues. The model performs a spatial and temporal analysis to highlight aspects of water scarcity by estimating surface flows and groundwater availability, and by modelling water demands based on demographic and industrial data. Moreover, it enables the simulation of various scenarios, including climate change, population growth, and economic development, to project future water resource conditions.[89]

The latest version of the model, dubbed GWAVA-GW, introduces the improved groundwater scheme that boosts the precision of groundwater dynamics within the model. This upgrade includes comprehensive modelling of hydrological processes such as evapotranspiration, infiltration, runoff, and river routing, along with the portrayal of both natural and human-made water bodies and mechanisms.[90,93] Recent developments in GWAVA have focused on enhancing its representation of human influences and natural hydrological cycles. It includes a representation of groundwater abstraction and artificial recharge, grounded in the principles of the AMBHAS-1D model. Additionally, the model integrates features such as check dams, farm bunds, and urban tanks to more accurately simulate small-scale hydrological interventions.[94]

5.2.12 The ChimERA. The ChimERA fate model, developed as a dynamic multimedia environmental model, offers a robust tool for assessing the spatial and temporal variability of chemical bioavailability in freshwater systems.[95] This model, recently updated to include dynamic environmental scenarios, represents a significant advancement in environmental risk assessment.[96] By integrating ecological parameters such as phytoplankton biomass, detritus, and dissolved organic matter (DOM), ChimERA provides a more ecologically realistic framework for modelling the fate of hydrophobic chemicals in aquatic environments. This is particularly important in scenarios where the chemical fate is influenced by seasonal and regional ecological processes, which are typically overlooked by traditional steady-state models.[95,96] ChimERA also consider the binding of organic chemicals to dissolved organic carbon (DOC) through a specified DOC partitioning parameter.

At the core of the ChimERA fate model is its ability to simulate chemical exchange between water and phytoplankton, incorporating adsorption, desorption, uptake, and depuration processes that are critical for understanding bioavailability. This is coupled with the modelling of detritus and DOM dynamics, which further influence the fate of hydrophobic chemicals by affecting their distribution between water, particulate matter, and sediments.[96] The inclusion of these factors allows ChimERA to provide a more nuanced assessment of chemical exposure, especially in shallow lentic systems, where organic matter plays a pivotal role in the sequestration and transport of pollutants.[97]

ChimERA's use of dynamic environmental scenarios for five distinct European regions—Mediterranean, Northern Italy, Central Europe, the UK, and Scandinavia—demonstrates how geographical and climatic differences affect chemical bioavailability. These scenarios take into account seasonal variations in water temperature, phytoplankton biomass, and organic carbon

content, providing a more accurate representation of how chemicals behave in different freshwater environments.[96] The model's findings highlight significant spatial variability, with bioavailable concentrations of chemicals being up to nine times higher in northern regions compared to southern ones, primarily due to differences in ecological dynamics.[95,96]

The ChimERA fate model's focus on dynamic, region-specific scenarios makes it a valuable tool for policymakers and environmental scientists aiming to understand the environmental risks associated with chemical emissions. Its comprehensive integration of ecological parameters sets it apart from more traditional models and offers a pathway toward more realistic and reliable assessments of chemical fate and exposure in freshwater environments.

5.3 Chemical models

5.3.1 MAMI. The MAMI model is a dynamic chemical speciation tool designed to investigate the complex chemical behaviours of neutral and ionizable molecules, including a wide range of chemical species such as bivalent acids and bases, amphoters, and zwitterions. Unlike exposure models, which primarily relate concentrations in environmental compartments to bioaccumulation and potential impacts on organisms, MAMI does not directly assess these aspects. Instead, it facilitates detailed speciation calculations within environmental compartments, such as air, various soil types, freshwater, seawater, and sediments, using chemical activity in water as its reference point. MAMI offers notably more fidelity to the speciation of organic chemicals than other models reviewed, by incorporating environmental factors like pH and ionic strength, offering a nuanced approach to modelling chemical dissociation and the effects of acidity and salinity on chemical behaviour.[39]

Distinct from the concept of fugacity, MAMI focuses on the activity of molecules or ions, encapsulating their free movement and serving as a guide to understanding thermodynamic equilibrium across charged and uncharged species. Through its calculations, the model reveals the impacts of environmental conditions on the transport and fate of chemicals, making it particularly suited for studying the behaviour of ionisable substances in various aquatic settings.[39] Despite its advanced approach, the current version of the MAMI model does not simulate how dissolved ions interact with solid surfaces or affect other solutes in water, highlighting areas for potential enhancement in future updates. Nonetheless, it overcomes the limitations of many other models in being able to accurately predict the speciation of ionisable substances.

5.3.2 SESAMe. The SESAMe model, developed by Zhu *et al.*, represents a fusion of the SimpleBox model's nested structure with the MAMI model's chemical speciation formulae, making it adept at handling both ionisable and neutral chemicals[98] with a dual-scale approach. It models environmental compartments on regional and continental scales and has currently been parameterised for China. Unlike the MAMI model, SESAMe includes additional compartments for vegetation, which are not a feature of MAMI, thereby enhancing its environmental modelling accuracy by considering more complex biotic interactions. SESAMe v3.0 advances beyond previous iterations by offering a finer spatial resolution of 50×50 km^2 and adding a seawater compartment, which extends the existing functionality seen in SimpleBox rather than merely duplicating it. This version also incorporates adjustments for temperature impacts on degradation rates and considers the influence of agricultural soil irrigation on transport processes. This addresses the need for greater spatial resolution over and above the local/regional/continental setup provided by SimpleBox.[98] Despite its advancements, SESAMe's primary limitation lies in its inability to simulate directional advective flow exchange between scales, restricting its capacity to track chemical movements across different regions.

5.4 Practical model selection for pharmaceuticals

SI Table 2 synthesises the criteria that are most useful in choosing which model to use for a particular scenario: spatial scale (from reaches to continental and global networks), temporal resolution (steady state *versus* time varying), explicit treatment of ionisation and pH-dependent speciation, representation of transformation products, consideration of optical and dissolved-organic-matter controls, and data demands. For reach-to-catchment-scale studies dominated by WWTP inputs, decision-oriented river models such as GREAT-ER, PhATE, or iSTREEM provide percentile PECs with modest input requirements.[10,11,43] When the priority is high-resolution mapping across large river networks under tight computational budgets, ePiE offers basin-to-regional coverage with good comparison against monitoring data.[42] For first-tier screening across different environmental compartments, multimedia box approaches like SimpleBox and, for lentic systems, QWASI, remain appropriate and transparent.[61,99] In systems where hydrodynamics, stratification, or light fields strongly modulate fate, like for deep lakes, reservoirs, estuaries, process-resolving frameworks such as WASP, AQUASIM, or QUAL-2K are preferable. Questions concerning continental-to-global patterns and policy levers are better served by GLOBAL-FATE, potentially interpreted alongside hydrological context from GWAVA. When speciation is determinative of exposure, particularly for ionisable pharmaceuticals. MAMI and the regionalised SESAMe provide pH-explicit assessments that can be coupled to routing models. Where bioavailability is shaped by biotic dynamics and DOM, ChimERA enables an integrated exposure–effects perspective. The table also records typical inputs and outputs, validation evidence, and known limitations, supporting transparent, fit-for-purpose selection and signalling when supplementary data or model coupling is warranted.

6 Medium effects on fate processes in pharmaceutical models

The physicochemistry of the environment (*e.g.* pH, soil or sediment organic matter content, temperature) strongly influences processes that control chemical fate, such as solid–solution partitioning and degradation. Pharmaceuticals, as part of

the broader category of anthropogenic organic chemicals, can be nonionisable or ionisable, with the latter's fate more sensitive to environmental conditions.

For nonionisable chemicals, the role of soil and sediment organic matter in controlling their partitioning between the porewater and the solid phase is well-established and accounted for in modelling using the organic carbon–water partition coefficient, K_{OC}. This coefficient may be estimated for a substance as a function of its octanol–water partition coefficient K_{OW}[100] if experimental data are not available. This model is broadly applicable and has been tested against experimental data (*e.g.* ref. 101), although it does have shortcomings, particularly where the organic matter composition includes significant amounts of 'black carbon',[102] which tends to bind nonionisable substances more strongly than do the widespread 'humic-type' components of natural organic matter.

This binding model can, however, show considerable shortcomings when applied to ionisable substances. Tolls (2001), in a review of the sorption of ionisable pharmaceuticals in soils, it was shown that partitioning-K_{OW} relationships for non-ionisable chemicals tended to severely underestimate the observed binding strength.[103] Tolls concluded that this underestimation was due to partitioning mechanisms such as surface complexation and hydrogen bonding, which are not relevant for nonionisable substances.[103] This key finding has been reinforced by other authors, *e.g.* Yamamoto *et al.* (2009) who showed that the partitioning of seven of eight ionisable pharmaceuticals was stronger than was predicted from their octanol–water distribution coefficients (D_{OW}).[104] On the other hand, Bronner and Goss (2011b)[101] were able to describe the variability in K_{OC} for a range of substances using a polyparameter, solvation energy approach based on the work of Abraham and coworkers.[105]

Approaches to modelling medium effects on the binding of ionisable substances have been developed. For example, Franco and Trapp (2008) developed a model for the normalisation of the soil–water partition coefficients for the ionised forms of a range of acids and bases to soil organic carbon content, using the pK_a/pK_b and K_{OW}.[40] This model has been incorporated into MAMI and SimpleBox 4.0. Franco, Fu, and Trapp (2009) extended the model to describe the pH–pH-dependence of soil partitioning for organic acids but found that their approach was not applicable to bases, because the pH-partitioning relationship differed from that for acids.[106]

Similarly, some models account for the association of organic chemicals with dissolved organic matter (DOM) in surface waters using the dissolved organic carbon partition coefficient (K_{DOC}). Examples of models discussed here that use K_{DOC} to model association with DOM are SimpleBox 4.0 and ePIE. Both these models use the formulation developed by Burkhard (2000) for non-ionisable compounds, to predict K_{DOC} as a function of K_{OW}.[41] Li *et al.* (2019) developed a model for K_{DOC} based on molecular connectivity factors with additional polarity correction factors for the influence of ionisable groups, focused on predicting a single K_{DOC} per substance across multiple substance groups.[107]

Vitale and Di Guardo (2019b; 2019a) reviewed existing models and data and proposed new models for partitioning nonpolar and acidic substances into DOC.[108,109] For nonionisable chemicals, they used a linear solvation energy relationship (LSER)[105] while for organic acids, they used a relationship based on the partitioning equations of Franco and Trapp (2008)[40] (log–linear relationships of binding for the neutral and ionised species to K_{OW}) and an LSER approach. The models generally fitted well; for organic acids, both the log–linear K_{OW} model and the LSER approach gave comparable results. However, significant relationships could not be found when applying these equations to organic bases, which parallels the findings of Franco *et al.* (2009) for soil partitioning.[106]

Medium influences on processes that break down a substance into different substances are also considered with varying degrees of complexity across the range of existing fate models. Recognising the potential contributions of multiple processes, such as hydrolysis, microbial degradation, and photolysis, to overall breakdown, some models allow separate simulations of breakdown processes. Other models combine individual processes into a 'lumped' breakdown rate. Models intended for screening-level assessment, such as SimpleBox 4.0 and PhATE, use a single ('lumped') breakdown process, typically employing first-order kinetics. More complex models intended to probe chemical behaviour in more detail, such as WASP and ePIE, employ process-specific kinetic breakdown rates. For example, GREAT-ER, WASP and ePIE allow for the effect of water pH on the rate of ionisable substance hydrolysis to be accounted for by specifying or estimating separate constants for neutral and ionised forms. These models can also account for the effect of water composition (*e.g.* the dissolved organic matter or suspended sediment concentration) on light attenuation, and thus on photodegradation rates.

These medium dependencies have direct consequences for model choice and parameterisation. For acidic *versus* basic pharmaceuticals, differences in soil/sediment binding and DOM association lead to distinct ranges of K_d/K_{DOC} and pH sensitivity.[40] When photolysis or hydrolysis exhibits diel-seasonal structure, models that resolve light attenuation and speciation—for example WASP, ePiE, or GREAT-ER—are preferable, whereas screening level frameworks such as SimpleBox or PhATE remain appropriate for bounding estimates when only lumped first-order loss is defensible. Where hazardous transformation products are plausible, workflows should (i) separate loss pathways to diagnose rate-limiting steps and (ii) enable follow-on transformation products exposure calculations, such as scenario branching or coupled modules.

7 Machine learning and AI tools for pharmaceutical fate and exposure modelling

Machine learning (ML) and artificial intelligence (AI) methods are becoming increasingly significant in modelling the fate and exposure of pharmaceuticals due to their proficiency in handling complex, high-dimensional, and heterogeneous

datasets.[110] Traditional environmental fate models, such as fugacity-based and spatially explicit chemical models, often struggle with extensive datasets and non-linear interactions, limitations that ML techniques effectively address. For instance, random-forest and support-vector-machine models have been successfully applied to predict the removal efficiencies and effluent concentrations of key pharmaceuticals in wastewater treatment plants,[111] and deep-learning frameworks have been used to reconstruct the spatiotemporal distribution of pharmaceutical residues in river networks at high resolution.[112]

Recent advancements highlight the application of various ML algorithms in the environmental modelling of micropollutants, pharmaceuticals, and emerging contaminants. ML and AI techniques have been increasingly applied to predict critical pharmaceutical fate and exposure modelling parameters, such as soil–water partitioning coefficients (K_d), aquatic toxicity, and contaminant distribution. Unlike traditional models like QWASI, SimpleBox, or PhATE, which rely on predefined physicochemical processes, ML models leverage large datasets to identify patterns and relationships without requiring explicit process-based assumptions. For instance, J. Li, Wilkinson, and Boxall (2021) developed ML-based models, including random forest (RF), artificial neural networks (ANN), and support vector machines (SVM), to estimate the partition coefficients of active pharmaceutical ingredients (APIs) in soils and sediments.[113]

Similarly, Garduño-Jiménez, Durán-Álvarez, and Gomes (2022) conducted a meta-analysis of batch-sorption studies and applied multivariate ML models to predict K_d for pharmaceuticals.[114] Their findings highlighted the importance of variables such as pharmaceutical solubility, soil organic carbon, and experimental conditions, demonstrating the ability of ML to integrate diverse data types for improved predictions. In aquatic toxicity modelling, Halder, Pradhan, and Cordeiro (2025) developed multitasking Quantitative Structure-Toxicity Relationship (mt-QSTR) classification models to predict whether a given pharmaceutical or personal care product would be "toxic" or "non-toxic", using a threshold derived from the ECOTOX database.[115] By employing both linear and nonlinear ML techniques within a Box–Jenkins moving-average framework, and further enhancing performance with consensus modelling, they achieved over 85% overall predictive accuracy. Their consensus modelling approach identified key molecular features, such as lipophilicity and molecular mass, driving toxicity.[115]

Recent studies also demonstrate that predictive accuracy and interpretability can be combined. Xu *et al.* (2025)[116] developed interpretable QSTR and q-RASTR models, supported by ML approaches, to predict the acute oral toxicity of quinoline-based pharmaceutical scaffolds. Their work not only adhered to OECD validation principles but also provided mechanistic insights into toxicity drivers, making the models both transferable and transparent. While outside the pharmaceutical domain, Chen *et al.* (2024)[117] presented a complementary example in which interpretable ML was used to predict oral toxicity of over 100 000 polychlorinated persistent organic pollutants (PC-POPs), showing how descriptor-based mechanistic explanations can enhance trust in high-throughput predictions. Together, these studies illustrate how advances in interpretable ML are beginning to bridge the gap between predictive performance and mechanistic credibility.

ML methods complement mechanistic fate and exposure models most productively where they supply or refine uncertain parameters, accelerate scenario analysis, and reconcile model outputs with monitoring data. For parameter inference, ML trained on batch-sorption compilations and wastewater-treatment datasets can provide priors for soil/sediment K_d and WWTP removal that are then propagated through established exposure models (*e.g.*, SimpleBox, ePiE, GREAT-ER, iSTREEM) when local measurements are sparse.[113,114] The resulting priors can be consumed by the model families already summarised in this review (screening *via* SimpleBox; high-resolution mapping *via* ePiE; reach-to-basin compliance *via* GREAT-ER; national-scale stewardship *via* iSTREEM).

A second integration pathway is probabilistic calibration, where monitoring data updates uncertain, process-specific rate constants (*e.g.*, photolysis, biodegradation) in models that resolve separate pathways; this yields posterior PEC distributions rather than single-value predictions. In parallel, surrogate modelling (emulation) can approximate outputs from large-scale exposure models (*e.g.*, GLOBAL-FATE or iSTREEM) to enable thousands of "what-if" runs for sensitivity and uncertainty analyses under treatment upgrades, demand-reduction scenarios, or low-flow extremes.

A third, operational coupling is data assimilation, whereby sequential river-concentration observations are blended with model forecasts to adjust emissions or dominant loss terms during events. Finally, interpretability and regulatory positioning merit explicit emphasis: despite strong predictive performance, ML is best used at present for parameter support, scenario screening, and emulation, while a documented mechanistic core remains the decision-critical artefact.

ML has also been applied to broader emerging contaminant fate modelling. Lei *et al.* (2023) reviewed ML applications for emerging contaminants, including pharmaceuticals, noting their effectiveness in predicting occurrence, distribution, bioeffects, and removal. Algorithms such as graph convolution and graph attention mechanisms have shown exceptional predictive power with high-quality datasets, though they are sensitive to data noise.[110] These advancements complement traditional models like GREAT-ER or iSTREEM by offering flexibility in handling unstructured data and complex environmental scenarios.

Despite their promise, ML and AI models face challenges, particularly in uncertainty quantification and interpretability. Ahkola *et al.* (2024) noted that both traditional and ML models struggle with comprehensive uncertainty analysis due to incomplete process representation and data variability.[118] ML models, in particular, can be less interpretable, as their outcomes are often driven by complex, non-linear relationships that are difficult to translate into practical insights. Additionally, the performance of ML models is highly dependent on

dataset size and quality, with noise and errors posing significant risks.[110]

8 Discussion and future directions

Pharmaceutical contaminants in the environment have the potential to cause significant impacts on ecosystems and human health. Modelling their fate and exposure enhances our ability to assess and mitigate these risks prospectively. However, the field faces challenges and opportunities to improve the accuracy and fidelity of these models. To tackle these challenges, it is essential to examine both the limitations of current approaches and the promising avenues for future improvements.

One of the primary challenges lies in simulating the complex interactions between pharmaceuticals and heterogeneous environmental media. Current models often simplify or use constant values for influential factors such as pH, temperature, and organic matter content. Bioavailability to biota[119,120] and dissolved organic matter[121] similarly depend on these variables, suggesting that consistent approaches for both fate and uptake models would improve risk assessment. Recognising these limitations leads to a broader discussion about model complexity and the balance between simplicity and mechanistic detail.

Model complexity should align with modelling objectives and data availability.[43] Screening-level models such as SimpleBox consider environmental compartments (*e.g.* soil types, freshwater, estuarine, or saltwater environments) as homogenous, whereas higher-tier models consider spatiotemporal variability within compartments. This perspective on complexity naturally prompts a comparison with modelling approaches used for other substances, such as metals. Historic research into the processes controlling metal fate has resulted in the development of complex mechanistic models for their reactions with natural organic matter[122,123] and other environmental components.[124] This focus has been enabled by the relatively small number of metals, compared to the thousands of pharmaceuticals typically modelled using simplified parameters such as K_{OW}. A major limitation is the lack of data on how pharmaceuticals degrade in the environment. This data gap limits the ability of models to predict the long-term fate and possible transformation products of pharmaceuticals, which may have different, potentially elevated toxicities compared to the original compounds. Current models also have difficulty in predicting or providing data to facilitate predictions of how pharmaceuticals accumulate and magnify in wildlife and humans, because of the complex factors that affect bioaccumulation, such as the compound speciation and organism biological traits. Addressing these data gaps is therefore a critical step toward enhancing model usefulness.

Improving predictions for ionisable substances, particularly organic bases, may require a deeper mechanistic understanding like that applied in metal speciation research. Current theoretical understanding of ionisable chemical behaviour presents a complex set of possible binding behaviours based on their ionisation properties.[125] Modelling of such effects to date has focused on interactions with organic matter, but has not captured key influences on binding and partitioning behaviour, especially for organic bases.[106,108] Current models primarily rely on pK_a-based relationships, but sometimes fail to capture key partitioning behaviours.[106] A better understanding of substance binding to individual environmental media components (organic matter, clays, minerals) may help to enhance model accuracy and explain the differing trends in binding with medium composition that are seen for different substances.[125] While such detailed mechanistic approaches are resource-intensive, insights from selected "model" substances could help inform the design of simpler, standardised tests. Integrating these insights into broader testing strategies would ultimately enhance cross-substance interpolation and the predictive power of fate models.

In terms of model complexity, while it is often desirable to develop more comprehensive and integrated models that consider detailed environmental processes (*e.g.*, advanced degradation kinetics, pH-dependent speciation, and effects of soil organic matter), the level of complexity needed ultimately depends on the purpose of the modelling exercise. Many existing models already account for medium-specific parameters, such as partitioning influenced by organic matter content or temperature, and the most advanced models incorporate pH-dependent behaviour. Improvements are particularly needed for ionisable substances, especially bases, rather than universally increasing complexity. Recognising these nuances is key to aligning model complexity with research objectives and available data.

The use of machine learning and artificial intelligence techniques has the potential to analyse complex data, such as large datasets of environmental parameters, emissions, and chemical properties, and to identify relationships and improve the accuracy of models. Recent developments demonstrate that ML can effectively predict the environmental fate and toxicity of pharmaceuticals by identifying key variables, such as soil characteristics, pharmaceutical properties, and experimental conditions. However, despite their strengths, ML models face challenges related to interpretability and transparency, limiting their direct regulatory use. Future directions should therefore focus on developing more interpretable and transparent ML models, improving data quality, and integrating ML techniques with conventional mechanistic models to leverage the strengths of both approaches.

Several priorities emerge for making exposure assessments of pharmaceuticals more reliable and policy and management-relevant. Foremost is improved treatment of ionisation, especially for organic bases, where persistent biases in K_d and K_{DOC} arise from incomplete mechanistic data and simplified sorption formalisms. Targeted datasets across relevant soils and sediments, including mineral- and clay-specific interactions, would allow models to separate electrostatic and hydrophobic contributions and to propagate pH-dependent speciation consistently through fate calculations. In parallel, routine representations of optical and seasonal drivers such as light attenuation, temperature, and diel/seasonal pH should be standardised across river and lake models so that photolysis and hydrolysis are handled

with comparable transparency and, where possible, constrained against monitoring.

A second, closely related need is explicit handling of transformation products. Generic "lumped loss" terms obscure which pathways dominate under given conditions and prevent propagation of transformation product exposures alongside their parents. Shared, modular transformation product components—covering conjugate cleavage, photo-products, and biologically mediated transformations—together with branching workflows that carry transformation product mass and uncertainty through the river network, would align exposure modelling with current analytical capabilities and hazard assessment practice.

Progress also depends on community infrastructure. Harmonised benchmark catchments with emissions, flows, and monitoring distributed with model-ready inputs would enable reproducible, like-for-like comparisons across tools. Accompanying FAIR (findable, accessible, interoperable, reusable) parameter sets, versioned code, and common evaluation metrics (including uncertainty reporting) would reduce duplication and increase transparency. To lower barriers to adoption of probabilistic analyses, openly available emulators and Bayesian calibration templates should be provided alongside widely used models (GREAT-ER, PhATE, iSTREEM, ePiE, GLOBAL-FATE), allowing rapid sensitivity analysis, scenario exploration, and principled uncertainty quantification without bespoke method development.

Finally, coordinated interdisciplinary collaboration is essential. Formal consortia spanning hydrology, environmental chemistry, microbiology, and machine learning can deliver time-bound, practical outputs. For example, an initial transformation-product module released with validated test cases; a pan-European river benchmark package with curated inputs, hydrology, and observations; and reference implementations of emulation and Bayesian calibration workflows. Together, these shared assets would establish a common testbed for method evaluation, enable transparent regulatory review, and expedite uptake in risk assessment and water-quality management.

9 Conclusion

Pharmaceuticals are a key group of environmental contaminants that require careful research on their fate and exposure to humans. This paper has provided a comprehensive overview of the methodological approaches used to model the fate and exposure of pharmaceuticals in the environment, highlighting the significance of understanding the sources, behaviour, and impacts of these contaminants. By systematically reviewing existing models, this study has revealed the challenges of forecasting pharmaceutical fate and exposure, which depend on factors such as chemical properties, environmental conditions, and biological interactions.

The review has also identified limitations of current models, such as the lack of data on degradation pathways, the complexity of modelling environmental interactions, and the difficulty of linking exposure levels to ecological and human health effects. Despite these limitations, the paper has suggested potential ways to improve the field. These include creating more advanced models that include detailed environmental processes, collecting and sharing more data, integrating ecotoxicological data, and using machine learning and artificial intelligence techniques.

Moreover, the importance of cross-disciplinary collaboration has been emphasised as a crucial element for future progress. By bringing together expertise from various fields, it is possible to develop innovative solutions that are more reflective of the multifaceted nature of pharmaceutical contamination in the environment.

In conclusion, while considerable progress has been made in understanding and modelling the environmental fate and exposure of pharmaceuticals, this field is still changing and developing. Ongoing research and innovation are vital to address the remaining gaps and challenges and to enhance our ability to evaluate and reduce the risks posed by pharmaceutical contaminants. The findings of this review not only add to the scientific knowledge of pharmaceutical fate and exposure but also highlight the need for effective management strategies and policy actions to safeguard environmental and public health. As we move forward, the scientific community must continue to pursue our knowledge and skills in this important area of environmental science. Overall, the modelling tools are decision-support tools. They structure knowledge and uncertainty to guide monitoring and management, rather than provide definitive predictions in isolation.

Author contributions

CU: conceptualisation, methodology, writing – original draft, review, and editing. SL and SH: funding acquisition, conceptualisation, supervision, formal analysis, writing – original draft, review, and editing.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

Supplementary information (SI) accompanying this article includes two tables: SI, Table 1, which provides a review of existing environmental exposure models for pharmaceuticals, and SI, Table 2, which presents a model selection matrix summarising pharmaceutical-specific modeling capabilities. See DOI: **https://doi.org/10.1039/d5em00449g**.

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