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Co-developing frameworks towards environmentally directed pharmaceutical prescribing in Scotland – A mixed methods study

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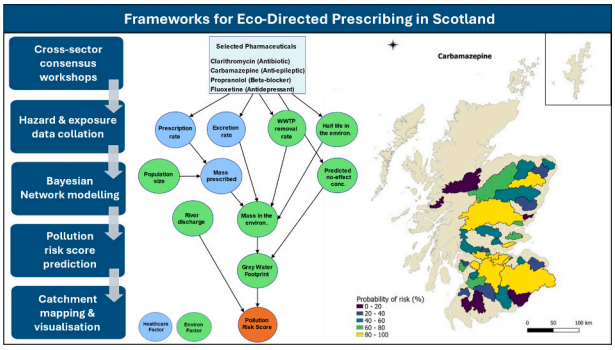
HIGHLIGHTS

- The study explored environmentally informed prescribing to reduce pharmaceutical pollution.
- The methods integrated public health, environmental modelling, and health services research.
- Pollution risk was predicted for four pharmaceuticals, with highest risk for clarithromycin.
- Maps visualised the probability of 40 freshwater catchments exceeding the predicted risk scores.
- This novel method seeks to incorporate environmental data into healthcare decision-making.

GRAPHICAL ABSTRACT



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ABSTRACT

The presence of human pharmaceuticals in the aquatic environment is recognised internationally as an important public health and environmental issue. In Scotland, healthcare sustainability targets call for improvements to medicine prescribing and use to reduce healthcare's impact on the environment. This proof-of-concept study aimed to develop a framework on the environmental impact of pharmaceuticals to use as a knowledge support tool for healthcare professionals, focussing on pharmaceutical pollution. Nominal Group Technique was applied to achieve consensus on pharmaceuticals and modelling factors for the framework, working with a panel of cross-sector stakeholders. Bayesian Belief Network modelling was applied to predict the environmental impact (calculated from hazard and exposure factors) of selected pharmaceuticals, with Scotland-wide mapping for visualisation in freshwater catchments. The model calculated the pollution risk score of the individual pharmaceuticals, using the ratio of prescribed mass vs. mass that would not exceed the predicted no-effect concentration in the freshwater environment. The pharmaceuticals exhibited different risk patterns, and spatial variation of risk was evident (generally related to population density), with the most catchments predicted to exceed the pollution risk score for clarithromycin (probability >80 % in 35 of 40 modelled catchments). Simulated risk scores were compared against observed risk calculated as the ratio of measured environmental

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concentrations from national regulatory and research monitoring and predicted no-effect concentrations. The model generally overpredicted risk, likely due to missing factors (e.g. solid-phase sorption, temporal variation), low spatial resolution, and low temporal resolution of the monitoring data. This work demonstrates a novel, trans-disciplinary approach to develop tools aiding collation and integration of environmental information into healthcare decision-making, through application of public health, environmental science, and health services research methods. Future work will refine the framework with additional clinical and environmental factors to improve model performance, and develop electronic interfaces to communicate environmental information to healthcare professionals.

1. Introduction

The prescription of a medicine (pharmaceutical) to diagnose, prevent, treat or cure disease is the most common medical intervention in healthcare, and is crucial to the health and wellbeing of modern society. Global medicine consumption is increasing, driven by factors such as climate change, aging populations, the prevalence of chronic diseases, and a growing "pill for every ill" culture (Busfield, 2010; Redshaw et al., 2013). Over 100,000 t of pharmaceutical products are consumed globally each year, with Europe accounting for 24 % of this total (Federation of European Academies of Medicine, 2022). However, this activity can negatively impact the environment through increasing carbon emissions and contributing to pharmaceutical pollution (Romanello et al., 2023; Thornber et al., 2022; Wilkinson et al., 2022). Significant attention has been given to reducing carbon emissions in the healthcare sector, including >50 countries signing the first Health Programme at the 26th United Nations Climate Change Conference of the Parties (COP26; Alejandre et al., 2023). There has been insufficient action to address the environmental impact of healthcare on water systems through pharmaceutical pollution – despite the potential risks to aquatic organisms and biodiversity, drinking water quality, soil and food chains, and contribution to the spread of antimicrobial resistance (AMR) (Moermond et al., 2023; Wilkinson et al., 2022).

Chemical pollution is recognised as a planetary crisis comparable to climate change and biodiversity decline (Ågerstrand et al., 2023). Human pharmaceuticals significantly contribute to global chemicals pollution in the environment, particularly water (wastewater, surface water, ground water, drinking water, sediments) and soil (agricultural land) (Boxall et al., 2022; Gunnarsson et al., 2019; Wilkinson et al., 2022). In Europe, the primary pathway of human pharmaceuticals into the environment is via urban wastewater. However, manufacturing practices, combined sewer overflows, and diffuse routes (e.g., septic tanks, land-applied sewage sludge) also significantly contribute to the environmental loads of pharmaceuticals in some locations (Dusi et al., 2018; Wilkinson et al., 2022). Pharmaceuticals are introduced into urban wastewater following patient ingestion and excretion (0–100 % of an orally administered medicine is excreted in an unmetabolized form), improper disposal (flushing down sinks/toilets) and washing off topically applied medicines (Helwig et al., 2023). Urban wastewater treatment cannot fully eliminate pharmaceuticals, metabolites, and transformation products from wastewater, with removal ranging from 0 to 100 %, depending on the specific compound, the wastewater treatment process and other environmental conditions (Comber et al., 2019; Niemi et al., 2020; Verlicchi et al., 2012). As a result, a diverse mixture of pharmaceuticals are discharged into surface waters (rivers, lakes, estuaries) with wastewater effluents, and >992 pharmaceutical compounds were reported in surface waters globally (Dusi et al., 2018; UBA, n.d.). Pharmaceuticals often remain biologically active after wastewater treatment and have been linked to adverse effects in non-target organisms. These include feminisation of male fish due to exposure to synthetic estrogen hormones (Baynes et al., 2023), and physiological and behavioural changes in aquatic species due to exposure to antidepressants (Weinberger and Klaper, 2014), antiepileptics (Lamichhane et al., 2013) and antianxiety medicines (Hellström et al., 2016). Antibiotics and other antimicrobials in the environment may also promote the development and spread of AMR, potentially undermining the efficacy of antibiotics in treating and preventing infections (Stanton et al., 2022). The direct risks to human health through environmental exposure to pharmaceutical pollution remain unclear, although in countries with sufficient sanitation and drinking water treatment, risks via drinking water uptake are negligible. A global study of 258 rivers from >100 countries found that concentrations of at least one pharmaceutical at >25 % of the monitored sites exceeded environmental thresholds pertaining to expected ecotoxicological endpoints or towards development of AMR, concluding that pharmaceutical pollution poses a risk to aquatic ecology and human health (Wilkinson et al., 2022).

The European Green Deal has spurred revisions in the EU Urban Wastewater Treatment Directive (UWWTD) and Environmental Quality Standards (EQS), designating a set of pharmaceuticals as priority substances for monitoring in wastewaters and surface waters (European Commission, 2022b). The proposed UWWTD will mandate advanced wastewater treatment to reduce pharmaceuticals in urban wastewaters, with the pharmaceutical and cosmetics industries covering 80 % of the costs under the "polluter pays" principle. However, pharmaceutical pollution is a complex challenge spanning many sectors and stakeholders, and addressing it will require interventions across the entire pharmaceutical lifecycle – from design and manufacturing, to prescribing and use, to disposal and waste treatment (OECD, 2019). The One Health concept provides a strategic framework to enhance collaboration across sectors, stakeholders and nations to tackle and prevent global crises at the interface between human-environment-animal health like chemical pollution and AMR (European Chemicals Agency, 2024). The One Health concept can foster innovative and sustainable solutions in healthcare by promoting "upstream", source-directed and user-oriented mitigation practices (e.g., health promotion, improved medicine selection, use, and disposal) and whole-systems thinking to develop interventions across the pharmaceutical lifecycle (Daughton, 2014; Helwig et al., 2023; Wang et al., 2024).

In the United Kingdom (UK), healthcare sustainability targets call for improvements to prescribing and medicine use (NHS England, 2022; Royal Pharmaceutical Society, 2021; Scottish Government, 2022a), as current practices are environmentally, economically, and clinically unsustainable – and healthcare has a social and moral responsibility to reduce its environmental impact. The National Health Service (NHS) spends >£20 billion/yr on medicines, with unused or partially used medicines costing ~£300 million – a significant waste symptomatic of the wider imprudent administration of healthcare (Daughton, 2014; Royal Pharmaceutical Society, 2021). Environmentally informed "eco-directed" prescribing may be an effective upstream mitigation strategy which could significantly reduce entry of targeted pharmaceuticals into the environment, coupled with reductions in whole-system costs and carbon emissions related to pharmaceutical manufacturing, transport, and use (Alejandre et al., 2023; Thornber et al., 2022). However, to promote more eco-directed prescribing and medicine use, healthcare professionals require robust, comprehensive, and accessible information on the environmental impact of pharmaceuticals to consider in decision-making (e.g., health technology assessments, national and regional medicine formularies, prescriber guidance) (Alejandre et al., 2022; Daughton, 2014; Toolan et al., 2023). Publicly available databases exist with environmental information of pharmaceuticals on national markets

for consideration in prescribing decisions, including the Swedish Pharmaceuticals and Environment (Janusinfo.se) and Norwegian pharmaceutical specialties website (Felleskatalogen.no) (Ramström et al., 2020; Welch et al., 2023). These compile the environmental risk and hazard of pharmaceuticals to support more environmentally-informed prescribing, following clinical and cost considerations. However, the availability, accessibility, and interpretation of such data remains a challenge for healthcare regulators and professionals, patients and other stakeholders (Linder et al., 2023).

In Scotland, stakeholders across the environment, healthcare and water sectors are collaborating to develop the national understanding of pharmaceutical pollution in the water environment, by forming the One Health Breakthrough Partnership (OHBP, https://ohbp.org). This study aimed to use the OHBP's pre-existing networks and resources to develop a framework on the environmental impact of selected pharmaceuticals to use as a knowledge support tool, with a focus on pharmaceutical pollution in the Scottish aquatic environment. A mixed methods approach was trialled through structured consensus developmental methods and environmental modelling, following a classification system based on human pharmaceutical prescribing data, ecotoxicological data, environmental monitoring data, and physicochemical data. To our knowledge, this is the first application of these techniques with regards to pharmaceutical pollution in the Scottish water environment, and a first application in the UK to develop a framework collating environmental impact data on pharmaceuticals to inform healthcare professionals.

2. Methods

2.1. Stakeholder mapping

Purposive sampling was used to approach stakeholders with knowledge of the environmental impact of pharmaceuticals, and who could provide information on the manufacturing, environmental risk assessment, licensing, health technology assessment (HTA) and formulary development processes for pharmaceutical regulation and prescribing. Scottish stakeholders were targeted – however, UK-wide policy and healthcare organisations were also approached. The mapping identified professionals across the healthcare, prescribing, public health, medicines regulation, pharmaceutical industry, water and environment sectors, as well as researchers in environmental science, pharmaceutical pollution and antimicrobial resistance. This included representatives from the researchers' networks, the Project Stakeholder Group, and the established networks of the Scottish OHBP. Stakeholders were approached via email with the Participant Information Sheet (detailing the research study, and workshop aims and methods), expected time commitment, and consent form. If willing and able to participate, stakeholders were invited to the virtual workshops (MS Teams). The number of active participants was limited to one representative per organisation to reduce bias/pressure from any individual agency. However additional participants were invited in an "observer" status if necessary.

2.2. Consensus workshops

A modified version of Nominal Group Technique (NGT) was used for the stakeholder workshops (Fig. 1) to consider the environmental and clinical perspectives in selecting both pharmaceuticals and framework criteria. NGT has four main stages (silent generation, round robin, clarification and voting/ranking). Here, Stage 1 was modified to use an online questionnaire (Qualtrics) for the silent generation, round robin and ranking to score the initial level of agreement (see Table S1). The questionnaire gathered personal information (name, job title, affiliation, sector), and included ranking and open-ended short-answer questions to assess the level of agreement with 14 shortlisted pharmaceuticals (Part A. Pharmaceutical selection), and environmental and clinical framework criteria (Part B. Framework criteria). It was developed through literature review, considering the baseline assessment of pharmaceuticals in Scotland's water environment (Helwig et al., 2022), report on eco-directed prescribing in Scotland (Alejandre et al., 2022), and the Priority Substances Directive list (European Commission, 2022b). Participants could complete the questionnaire with colleagues within their organisation, but only one representative could actively participate in the workshops. Prior to the workshops, each participant was presented with a Personal Form comparing their individual responses to anonymous group aggregated responses to discuss their opinions and points of disagreement (if applicable). Participants attended two 3-hourh online workshops (Stages 2–-4) to reach consensus separately on the pharmaceutical selection (Part A) and framework criteria (Part B):

- Stage 2 – clarification and focus group discussion addressed points of disagreement from the questionnaire (Stage 1). The list of pharmaceuticals, or framework criteria were updated as needed.

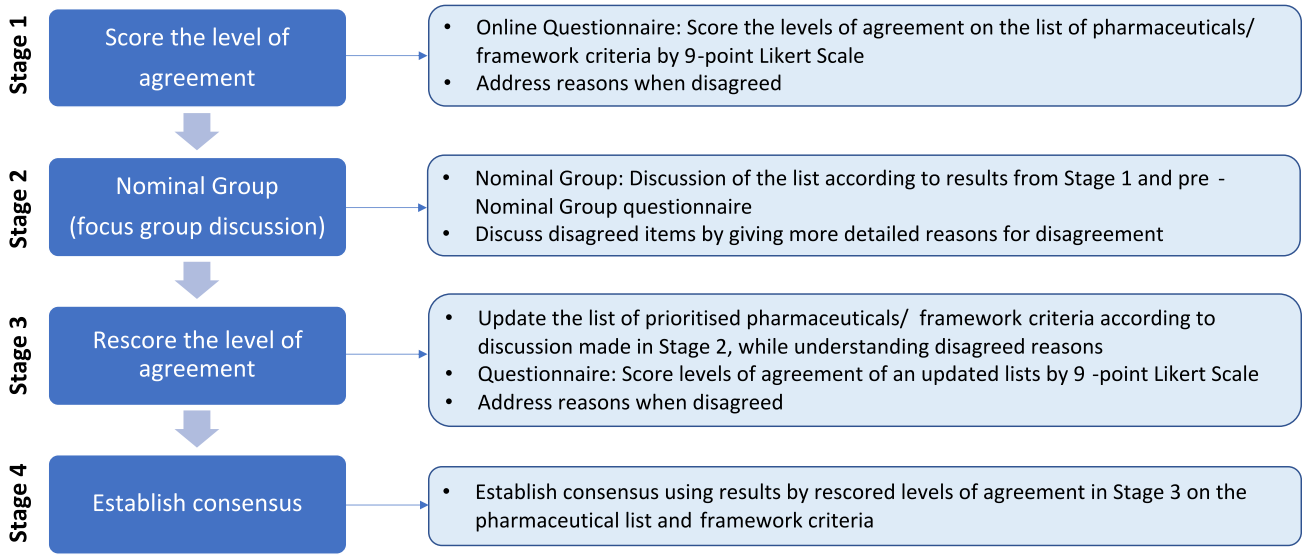

Fig. 1. Flow diagram showing the four stage Nominal Group Technique (NGT) that was applied to select the pharmaceuticals and framework criteria for inclusion in the knowledge support tool.

- Stage 3 – participants were presented with the updated lists, and ranking was performed to re-score the level of agreement. Facilitated discussion followed, with Stages 2 and 3 repeated as necessary to establish consensus.
- Stage 4 – consensus established, with the levels of agreement determined using 9-point Likert scale (equally valued), and agreement was predetermined as a group median between 7 and 9, an interquartile range of <3, and as no participant scoring ≤3.

Facilitators controlled the discussion at each stage to provide equal opportunity for participants to voice opinions. Workshop outputs were thematically analysed.

2.3. Database collation

Through stakeholder consultation and interrogation of data sources, a database was developed collating information on the selected pharmaceuticals and framework criteria. Various resources were assessed (e.g., peer-reviewed literature, open-access databases, and regulatory data) to access information on pharmaceutical prescribing in Scotland, and environmental hazard and exposure factors (see Table S2). Ecotoxicological and physicochemical databases were accessed (NORMAN database, the US Environmental Protection Agency's (EPA) EPA EPI Suite, EPA ECOTOX Knowledgebase, EPA CompTox Chemicals Dashboard, PubChem, ChemSpider, OECD eChem Portal). As were resources from the European Medicines Agency (EMA) and pharmaceutical industries, including environmental risk assessments (ERAs) and product specification sheets (FASS.se; AstraZeneca; AMR Industry Alliance). Georeferenced community prescribing data (population and mass standardised) from Public Health Scotland was accessed for years 2015–2022 through the *Pharmaceuticals in the Environment* database, hosted by the Scottish Environment Protection Agency (SEPA) on behalf of the OHBP (SEPA, 2022). Scottish georeferenced measured environmental concentrations (MEC) were accessed from the SEPA database, representing >48,000 datapoints for years 2014-present from published, regulatory and grey literature (SEPA, 2022). The regulatory MEC data originates from SEPA and Scottish Water's monitoring through the Chemicals Investigation Programme in Scotland (CIP; Phases 2 and 3; SEPA, 2022). The average WWTP removal rates were determined for Scottish WWTPs where paired sampling was performed for both the influent and effluent wastewater, and where n number of samples was >3 and >75 % of concentrations were reported as a discrete value (i.e., a numeric value >1/2 the limit of detection, as presented by Scottish Water).

2.4. Environmental risk modelling

The database was integrated into a holistic model framework using a hybrid Bayesian Belief Network (BBN). BBNs are probabilistic graphical models that allow integration of diverse data in a trans-disciplinary framework, while accounting for uncertainty (Pearl and Mackenzie, 2018). Their intuitive graphical nature lends itself to model co-development with stakeholders, thus increasing the credibility of modelled outcomes (Moe et al., 2021). Causal networks developed using expert knowledge can be applied to simulate hypothetical 'what-if' scenarios in situations where controlled experiments may not be possible and data may be scarce (Pearl and Mackenzie, 2018). Here, the conceptual model structure was developed with experts and stakeholders in GeNIe modeller vs 4.0 (https://www.bayesfusion.com/genie/). The model was parameterised using both data and literature. Statistical distributions, representing uncertainties, were fitted to available data using the *fitdistrplus* package in the R statistical environment vs. 4.2.3 (Delignette-Muller et al., 2015). Predicted environmental concentrations (PEC) were calculated based on physicochemical properties (half-life in the environment), national prescribing data, excretion rates, and wastewater treatment removal rates. Subsequently, three risk scores were calculated. Firstly, the Grey Water Footprint (GWF) method was adapted, which represents water pollution in volumetric terms to estimate human pharmaceutical loads entering surface water from WWTP point-sources (Wöhler et al., 2020). GWF would then represent the volume of water needed to dilute pollution below safe levels (i.e. the predicted no-effect concentration, PNEC). Secondly, this approach was reformulated to suit the healthcare community to develop a risk ratio that represents the mass of prescribed medicines to the mass that would be 'safe' to dissolve in the available surface water in a catchment (mean annual discharge), without exceeding the PNEC (see Tables S3 and S4 for full description). Finally, PECs were compared to the PNECs to calculate the risk quotient (RQ), here presented as the pollution risk score. The risk score quantifies the likelihood of the pharmaceutical exceeding the threshold level where eco-toxicological effects are expected, and risk scores were derived from PEC and MEC data to compare differences in potential risk between modelling and monitoring. Generally, a risk score > 1 is considered to indicate a potential concern towards ecotoxicological effects. Mathematically, all three risk scores are identical, while conceptually each may be more suitable to a different stakeholder group. The posterior probability of exceeding the risk score was based on stochastic sampling from the uncertain priors, using the clustering algorithm in GeNIe Modeller vs. 4. (https://www.bayesfusion.com/genie/). 10,000 model simulations were implemented in the R statistical environment vs. 4.2.3, using rSMILE vs. 2.0.10 (https://download.bayesfusion.com/files.html?category=Academia).

2.5. Mapping

Spatial processing and mapping were done in QGIS 3.22 (https://qgis.org). Maps were developed to show the probability of the individual Scottish catchments exceeding the risk score (i.e., RQ > 1). Population data from the 2021 Census was accessed from the National Records of Scotland (https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population, accessed 2023) by Data Zones (2011 revision, areas designed to have roughly standard populations of 500 to 1000 household residents). Maps were created by linking population data with the Data Zone boundaries included within the selected catchment areas (Spatial.Data.gov.scot, 2023). Mean annual river discharge was accessed from a published data set for 40 catchments in Scotland that had their outlet closest to the coastline, based on the National River Flow archive hydrometric observations from the UK (CAMELS-GB data set; Coxon et al., 2020).

3. Results

3.1. Consensus workshops

Mapping was performed to identify relevant stakeholders and experts across various sectors regarding pharmaceuticals in the aquatic environment and prescribing decision-making. In total 12 participants attended the stakeholder workshops (nine in the 1st meeting, and an additional 3 joined the 2nd meeting), representing: healthcare provision, prescribing, public health, medicines regulation, pharmaceutical industry, environmental regulation, water industry and research organisations. UK-wide pharmaceutical industry trade associations to identify individuals with knowledge/background on pharmaceuticals in the environment and ERAs, to avoid bias in private sector representation in the workshops. Additionally, multiple organisations in healthcare regulatory positions were approached at the UK level – however some organisations did not feel it would be appropriate or within their scope of knowledge to participate in the workshops.

Each participant completed the two-section pre-workshop questionnaire. The anonymous group aggregated questionnaire results are available in the Supplementary material (Table S1). Participants ranked the 14 pre-selected pharmaceuticals, and the shortlist did not reach consensus (median = 5.0, range = 3–9, IQR = 3.0) (Table 1). During the

Table 1
Pharmaceuticals shortlisted with Stage 1 (questionnaire) consensus outcome, and list of six which reached consensus (Stage 4) with notes on those selected for the modelling. IQR = interquartile range.

Consensus outcome	Pharmaceutical		Notes
Stage 1: Median = 5.0 (3–9) IQR = 3.0	17-alpha ethinylestradiol (EE2)	Diclofenac	*Consensus not reached*
	17-betaoestradiol (E2)	Erythromycin	
	Azithromycin	Metformin	
	Carbamazepine	Oestrone (E1)	
	Ciprofloxacin	Propranolol	
	Clarithromycin	Ranitidine	
		Triclosan	
Final Stage 4: Median = 8.0 (5–9) IQR = 1.25	17-alpha ethinylestradiol (EE2)		*Not selected due to lack of standardised prescription data*
	Azithromycin		*Not selected due to low prescribing rates in Scotland*
	Carbamazepine		
	Clarithromycin		
	Fluoxetine		*Added to list*
	Propranolol		

NGT workshops, which the participants discussed the key clinical and environmental factors to finalise selection of pharmaceuticals, in consideration of project scale (time and resources), data availability (both environmental and clinical) and other factors impacting prescribing and occurrence of pharmaceuticals in the water environment (i.e. vet/human sources, usage patterns, formulations, etc.). From the clinical perspective, the selected pharmaceuticals should be: human-use, prescription only medicines (POM), oral formulation, widely prescribed with community prescribing data available, and with an option for alternatives (pharmacological or non-pharmacological). From the environmental perspective, data availability in selecting the pharmaceuticals was a key consideration, including: Scottish MEC data (e.g., *Pharmaceuticals in the Environment* database; SEPA, 2022), ecotoxicological data (e.g., PNECs, Environmental Quality standards), wastewater treatment data (e.g., Scottish Water, CIP2 and CIP3 Scotland), physicochemical data (e.g., persistence, bioaccumulation, partitioning behaviour). During Stage 2 discussion, additional pharmaceuticals were suggested, including: antidepressants (fluoxetine, sertraline, citalopram, venlafaxine), antibiotics (trimethoprim, sulfamethoxazole), analgesics (naproxen, paracetamol), cytostatics (cyclophosphamide, ifosfamide), thyroid hormones (levothyroxine), dementia treatment (donezepil), proton pump inhibitor (omeprazole), and some pharmaceutical classes without specific names (see Table S1). Following Stage 3 voting and ranking, fluoxetine was added to the list as it was identified as a priority pharmaceutical from the environmental and healthcare perspectives. Consensus was established on a total of six compounds (median = 8.0, range = 5–9, IQR = 1.25), and of these, four compounds were taken forward by the research team considering the data availability.

The group reached consensus on the environmental impact criteria to include in the framework modelling (Table 2). The Stage 1 outcome (questionnaire) demonstrated that consensus was established on the proposed factors, however, additional environmental factors were suggested, including water solubility, mobility, no-effect concentrations (including end-point, test organism, exposure time for ecotoxicity tests), short-course vs long-term prescriptions, mixtures and synergistic effects, endocrine disruption, and metabolites/degradation products. Following discussion and voting (Stages 2 and 3), the list was re-evaluated to include water solubility, mobility, and metabolites/degradation products. The clinical factors (safety, suitability, clinical and cost-effectiveness) were discussed (Stage 2), however did not reach consensus due to time and resource limitations required for accessing and collating this data. The final consensus was established for the factors in Table 2 (median = 8.0, range = 5–9, interquartile range = 2.0).

Table 2
Environmental criteria with Nominal Group Technique Stage 1 (questionnaire) outcomes shown, and definitions and references. Additional factors are included which were put forward during the workshops (Stages 2 and 3). IQR = Interquartile Range.

Criteria	Stage 1 Consensus outcome	Definition (reference)
Persistence	Median = 8.0 (4–9) IQR = 1.50	Half-life, physicochemical property to determine resistance to naturally occurring biodegradation in environmental media [A] (here water)
Bioaccumulation	Median = 8.0 (4–9) IQR = 1.50	Octanol-water partition coefficient, physicochemical property to determine potential to accumulate in tissue (lipophilicity) [A]
Water solubility	Additional factor	Physicochemical property to determine how miscible the compound is with water (hydrophilicity) [A]
Mobility	Additional factor	Organic carbon-water partition coefficient, physicochemical property to determine potential sorption to sediments/soils (high mobility indicates likelihood to be transported through solid phase) [A]
Predicted No-Effect Concentration	Median = 8.0 (5–9) IQR = 2.50	PNEC, the threshold (concentration) below which no toxicological effects occur, usually derived through acute toxicity exposure studies against three trophic levels of aquatic organisms [B]
Minimum Inhibitory Concentration or Minimum Selective Concentration	Median = 8.0 (6–9) IQR = 2.00	Lowest threshold (concentration) at which inhibition of bacterial growth occurs (MIC) or selection of antimicrobial resistance genes (MSC) in microorganisms [C]
Prescription volumes	Median = 7.0 (6–9) IQR = 1.50	Estimation of pharmaceuticals distributed and used in the community, by mass and population standardised
Excretion profiles	Median = 8.0 (5–9) IQR = 1.75	Estimated quantity of parent pharmaceutical excreted following metabolism (percentage)
Metabolites and degradation products	Additional factor	Acknowledging that some metabolites and degradation products retain the pharmacological activity of the parent compound, or have therapeutic effects
Wastewater treatment removal rates	Median = 7.5 (4–9) IQR = 1.75	Indicating the effectiveness of wastewater treatment to eliminate pharmaceuticals from final effluent, acknowledging that removal will vary by treatment type, and be influenced by environmental factors
Measured or predicted environmental concentrations	Median = 8.5 (5–9) IQR = 2.00	Pharmaceutical concentrations determined in surface water, using monitoring data or modelling

References: [A]Hale et al., 2020; [B]Helwig et al., 2022; [C]Murray et al., 2021.

The group discussed the principle of including environmental aspects of medicines in healthcare decision-making and prescription formularies (i.e., lists of approved medicines for prescription, regionally or nationally). And the roles of the Scottish Medicines Consortium (SMC) and

Area Drugs and Therapeutics Committees (ADTCs). Discussion ranged on the potential involvement of environmental scientists and ecotoxicity experts in the SMC and ADTCs during regulatory and healthcare decision-making. Consensus was reached amongst the stakeholders on the concept of including environmental information in prescribing formularies (median = 8.0, range = 6–9, IQR = 2.00), and developing knowledge support tools to inform healthcare decision-makers about the environmental impact of medicines (median = 8.0, range = 5–9, IQR = 1.25). However, agreement was not reached on involving experts from the environment sector in the SMC (median = 8.0, range = 1–9, IQR = 3.00), ADTCs (median = 8.0, range = 5–9, IQR = 3.50) and both the SMC and ADTCs (median = 8.0, range = 1–9, IQR = 3.25).

3.2. Environmental risk modelling and mapping

Data were collected on the environmental hazard and exposure factors of selected pharmaceuticals. Seven of the 11 factors which reached consensus were taken forward for data interrogation and collation (Table 3), with data used for model parameterisation in the Supplementary material (Table S4). The database was incorporated into a BBN Model to generate individual pollution risk scores for the four pharmaceuticals in freshwater catchments in Scotland.

The model was co-developed with the stakeholder group and experts, following the outputs from the consensus workshops. The causal model structure is shown in Fig. 2, displaying the healthcare (blue) and environmental (green) factors related to pharmaceutical exposure and potential effect in the water environment. The predicted pollution risk score is generated based on the amount of water required to dilute the pharmaceutical concentration below the PNEC, quantified through comparison of GWF (Wöhler et al., 2020) and the mean annual river discharge for the 40 individual catchments (Coxon et al., 2020). This risk score can also be expressed as the ratio of prescribed mass to 'safe' mass that would not exceed the PNEC, when diluted in the river basin using mean annual discharge. Thirdly, the same risk score can also be expressed as the ratio of predicted environmental concentrations (PEC) and PNEC. The model structure was developed for all compounds as independent sub-models, with example sub-model structure with input data for carbamazepine included in the Supplementary material Fig. S1. The predicted pollution risk score was compared to the observed risk score (based on MEC data) (Table 4). Where "below" and "above" indicate probability of the substance risk score exceeding 1. Considering the MEC, the observed risk was found to be low for all four pharmaceuticals, with >90 % probability that the pollution risk scores of the individual pharmaceuticals in the selected catchments are below the PNEC. Considering the predicted risk, clarithromycin was found to have the highest overall risk (94 % probability that the concentration will be > PNEC), followed by carbamazepine (53 %), propranolol (50 %), and fluoxetine (48 %).

Maps to visualise the predicted risk in 40 freshwater catchments in Scotland were prepared (Fig. 3). Here the maps are presented as a probability of a catchment exceeding the predicted pollution risk score, where risk score > 1 is considered a "risky" situation (closer to yellow). Clarithromycin was found to have the highest probability of exceeding the pollution risk score, with 35 of the 40 catchments with an 80–100 % probability of exceeding the risk score, four catchments with a probability of 60–80 %, and one catchment with <40 % probability. For fluoxetine 11 catchments had an 80–100 % probability of exceeding the risk score, 10 for carbamazepine and 8 catchments propranolol. The latter eight catchments were found in common for all four pharmaceuticals to have a high probability that the substance would exceed the risk score. See Supplementary material (Fig. S2) for a map of Scotland's geography, with the three largest cities displayed (population > 200,000, National Records for Scotland).

Table 3
Factors and data sources for modelling and mapping.

Factor	Data source(s) and references
Population	National Records of Scotland, accessed from https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/population
Prescription rate	Pharmaceuticals in the Environment tool (population and mass standardised), (georeferenced datasets accessed from SEPA, 2022, originating from Public Health Scotland Prescriptions in the Community dataset)
Excretion rates	Pharmaceutical company data sheets (FASS.se, AstraZeneca), peer-reviewed literature
Removal in WWTPs	Chemicals Investigation Programme Scotland (CIP2 and CIP3), calculated from MEC influent and effluent data (SEPA, 2022)
Half-life in the environment	NORMAN database "Substance factsheets" https://www.norman-network.com/nds/factsheets/show.php?susID=196, Pharmaceutical company data sheets (FASS.se, AstraZeneca), EPA database, peer-reviewed literature
Predicted no-effect concentration	EMA EPAR environmental risk sheets, and EU Priority Substances Directive (Appendix V, European Commission, 2022a), peer-reviewed literature
Minimum inhibitory concentration	AMR Industry Alliance, peer-reviewed literature
MEC	Pharmaceuticals in the Environment tool, (georeferenced datasets downloaded from SEPA, 2022)
Catchment boundaries and mean annual river flow from CAMELS-GB	Environmental Information Data Centre Accessed from https://doi.org/10.5285/8344e4f3-d2ea-44f5-8afa-86d2987543a9 (Coxon et al., 2020)

4. Discussion

4.1. Consensus workshops

A major challenge in promoting eco-directed medicines use in clinical practice is the inherent complexity and multidisciplinary nature of this field. As such, it was crucial to engage stakeholders across academia and the water, environment, pharmaceutical industry, public health and prescribing sectors. The NGT method provided a structured four-stage process to reach consensus between the stakeholders in selecting suitable pharmaceuticals and criteria to model for the framework. Stakeholder mapping identified the key specialists or professional categories. The selection of particular individuals was not found to significantly impact ratings, if specialists or professional categories were sought carefully based on the study aims (Hutchings and Raine, 2006). Through the NGT, varying perspectives were addressed following a structured process of group engagement with a maximum of 12 individuals, enabling strong engagement throughout the process (Black, 2006; Humphrey-Murto et al., 2017). The main advantages of NGT include the ability to obtain relatively quick outcomes, generate multiple ideas, and promote greater "ownership" of the decisions developed by participants, which can affect implementation of outputs post-study (Arakawa, 2022). Similar NGT approaches have been successfully applied elsewhere, including to develop healthcare guidelines and national frameworks (Hussain et al., 2022; Søndergaard et al., 2018).

The pre-workshop questionnaire (Stage 1) enabled quick identification of knowledge gaps and areas of disagreement, and the NGT method encouraged a wide ranging discussion during the workshop (Stages 2–3). Disagreement was largely driven by organisational priorities, competing interests or background expertise. There are >1900 medicines registered for human use in the UK (Thornber et al., 2022), and selecting realistic and workable pharmaceuticals in a timely manner was a key aim for the NGT workshops. Here, the Stage 1 questionnaire presented a shortlist of 14 pharmaceuticals, selected following literature

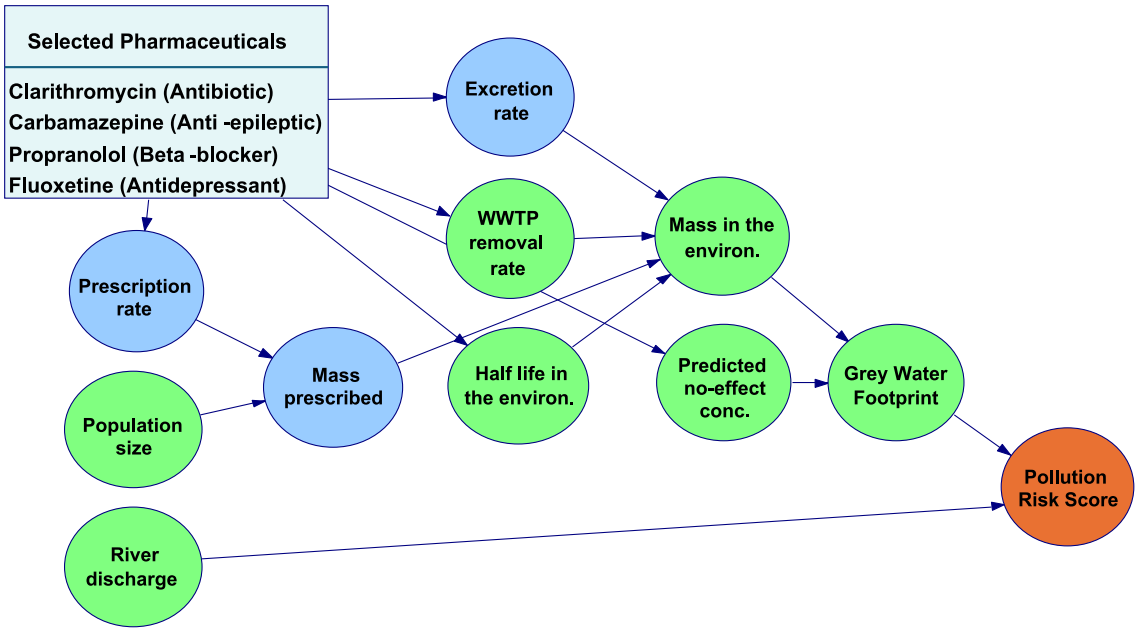

Fig. 2. Model structure displaying healthcare (blue) and environmental (green) factors used to generate the pollution risk score (orange) for the selected pharmaceuticals (individually) in freshwater catchments, by comparing the GWF and annual river discharge.

Table 4
Predicted and observed pollution risk scores for the individual pharmaceuticals in the modelled freshwater catchments, with PNECs. Where "above" indicates probability (%) of the substance risk score exceeding 1, and "below" vice versa.

Pharmaceutical	PNEC (μg/L)	Predicted Risk Score (based on PEC)	Observed Risk Score (based on MEC)
Carbamazepine	2.5[A, E, F], 2.0[G]	Below = 47 % Above = 53 %	Below = 90 % Above = 10 %
Clarithromycin	Ecotoxicity: 0.07[H], 0.08[B], 0.12[G]; 0.13[A], 0.25[C] AMR: 0.25[B,C]	Below = 6 % Above = 94 %	Below = 91 % Above = 9 %
Fluoxetine	0.047[D], 0.05[H], 0.1[G], 0.32[E, F]	Below = 52 % Above = 48 %	Below = 99 % Above = 1 %
Propranolol	0.1[D,J], 0.2[E], 0.23 [I], 0.24[H], 0.41[G]	Below = 50 % Above = 50 %	Below = 95 % Above = 5 %

Reference: [A] European Commission, 2022a; [B] tell et al., 2019; [C] AMR Industry Alliance, 2023; [D] SEPA, 2022; [E] Gunnarsson et al., 2019; [F] FASS, accessed 2023; [G] NORMAN, accessed 2023; [H] Verlicchi et al., 2012; [I] AstraZeneca, 2023; [J] Bouzas-Monroy et al., 2022.

review and relevance to the Scottish water environment, including:

- The review of pharmaceuticals in the Scottish water environment, including >48,000 MEC datapoints from research and regulatory monitoring. This identified pharmaceuticals with a higher ecotoxicological and/or AMR risk in inland surface waters, including ibuprofen, clarithromycin, erythromycin, diclofenac, EE2, metformin, ranitidine, propranolol and ciprofloxacin (Helwig et al., 2022).
- The proposed priority substance list and Environmental Quality Standards (EQS) in surface waters, including: EE2, E2, E1, clarithromycin, erythromycin, azithromycin, carbamazepine, diclofenac, ibuprofen, and triclosan (European Commission, 2022b).

The environmental experts were largely in agreement with the preselected 14 pharmaceuticals, and familiar with the sources used to compile this list. However, representatives from the healthcare sector who were less familiar with the environmental perspective identified additional pharmaceuticals of key interest regarding prescribing activity and usage patterns – and thus the list was refined based on clinical considerations (i.e., human-use, POM, widely prescribed in the community, oral formulation). Fluoxetine (an antidepressant) was proposed in Stages 2–3, as antidepressants prescribing is rising across Scotland with fluoxetine demonstrating a 14 % increase from 2017 to 2022 (SEPA, 2022). Although it should be noted that fluoxetine is also licensed for veterinary use in the UK, with 8 licensed products for dogs (chewable tablets) (Veterinary Medicines Directorate, accessed 2023). While the environmental impact of veterinary medicines is of scientific and regulatory interest, with topically applied parasiticides an important contributor to overall pesticide pollution in UK rivers (Perkins et al., 2021). Scottish veterinary sales/prescribing data was not accessible, and the environmental impact of antidepressants from companion animal usage was considered minimal compared to human usage. Of the six compounds which reached consensus (Stage 4), two (EE2, azithromycin) were not modelled. The synthetic estrogen EE2 is prescribed via multiple formulations with various administration routes (e.g., oral, topical, transdermal, intrauterine, subcutaneous injection and implant) and by various outlets (e.g., GPs, sexual health clinics) – and as such national-level usage is not well characterised and standardised prescribing data is not available (Public Health Scotland, 2023). And due to higher prescription rates, clarithromycin was selected over azithromycin, with average amount prescribed approx. 74.6 g and 23.5 g per day per thousand people in 2022, respectively (Public Health Scotland, 2023; SEPA, 2022).

The Stage 1 questionnaire also considered criteria for inclusion in the framework. Following consultation with NHS Scotland formulary and healthcare colleagues, and wider stakeholders, clinical factors were not included in the final version of the framework due to time and resource limitations in accessing and collating this data. The framework collated information on the environmental risk and hazard of pharmaceuticals in the water environment, which may be later compared with healthcare factors (e.g., clinical and cost effectiveness). Environmental hazard refers to the inherent environmentally harmful properties of a pharmaceutical, such as the ability to resist degradation (persistence), to accumulate in tissue (bioaccumulation), and the toxicity towards organisms and predominance towards driving AMR (Hale et al., 2020; Linder et al., 2023; Ramström et al., 2020). While environmental risk refers to the likelihood of toxic effects occurring in aquatic organisms (i.

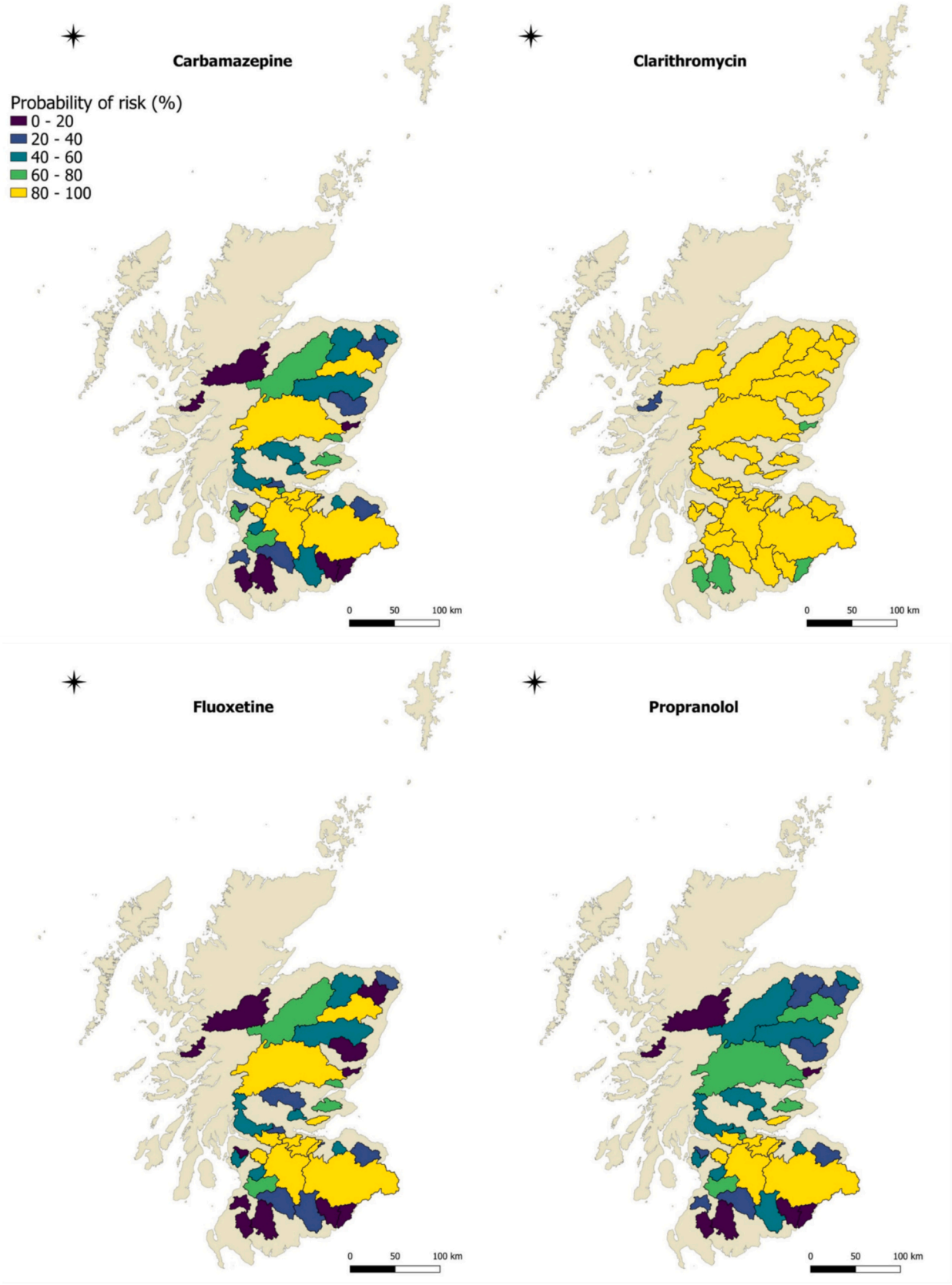

Fig. 3. Maps visualising the probability of modelled catchments exceeding the predicted pollution risk score in Scotland (risk score > 1), for the selected pharmaceuticals: carbamazepine (top left), clarithromycin (top right), fluoxetine (bottom left), propranolol (bottom right).

e., a comparison between exposure and toxicity), and is dependent on the pharmaceutical loads reaching the environment (Linder et al., 2023; Ramström et al., 2020). Both risk and hazard should be considered when evaluating the environmental impact of pharmaceuticals, and here consensus was established for 11 hazard and exposure factors. The selected factors are in line with other knowledge support tools such as the Swedish database *Pharmaceuticals and Environment* (Janusinfo.se; Linder et al., 2023), and those proposed in a UK eco-directed prescribing policy brief (Alejandre et al., 2023). However, the workshop participants discussed other aspects (both environmental and clinical) which would affect the usage and presence in the aquatic environment, such as short-course vs long-term prescriptions, metabolites and degradation products, mixture effects (i.e., if multiple compounds in the environment would exhibit synergistic effects), and the use of ecotoxicity data. The complexity due to availability, reliability, and robustness of eco-toxicity data was noted, and the usage of established PNECs and EQS (where applicable) were agreed, rather than the independently gathered eco-toxicity data (although this was included in the database following review of literature and public access data, see Supplementary material for information). Next stage would seek to perform an evaluation of ecotoxicity data of individual studies in comparison to the Criteria for Reporting and Evaluating ecotoxicity Data (CRED) and Klimisch method (Kase et al., 2016; Moermond et al., 2016).

4.2. Environmental risk modelling and mapping

The framework for the knowledge support tool was co-developed with stakeholders, using the agreed pharmaceuticals and criteria, underpinned by BBN modelling to generate a predicted pollution risk score and visualisation through GIS mapping. BBN modelling is an appropriate and useful technique to employ here, as it incorporates and captures uncertainties in causes and effects (e.g., pharmaceutical transport into the environment, environmental concentrations leading to environmental impact), which can be applied to complex scenarios (Moe et al., 2021). It has been successfully applied to improve environmental risk assessments and implementation in regulatory risk frameworks for chemicals, as well as to approve medical devices and assess medical diagnosis (Moe et al., 2021; Mentzel et al., 2022; Welch et al., 2023). Here we demonstrated the broad applicability of BBN methodology in risk-based environmental modelling and assessment, building on recent advancements of BBN in environmental risk assessments and promoting uptake and added value in healthcare and other sectors to address complex sustainability issues. The BBN modelling adapted the GWF method which represents water pollution in volumetric terms (Wöhler et al., 2020). The GWF for the individual pharmaceuticals was compared to river discharge (mean annual discharge, m^3/s) and available run off (m^3) in the modelled catchments to generate a pollution risk score based on the amount of water available/expected to dilute the PEC below the PNEC. The risk varied by compound, with clarithromycin demonstrating the overall highest probability of exceeding the pollution risk score (35 of 40 catchments, >80 % probability). This may be due to lowest overall removal rate of clarithromycin during WWT, with an average removal of −22.5 % ± 127.3 (ranging <−100 % to 75 %), calculated from 35 WWTPs in Scotland (n number of paired samples = 574), with 75 % of data demonstrating <35 % removal (Scottish Water, CIP2 and CIP3). Literature reports poor aqueous-phase removal of clarithromycin and other macrolide antibiotics, with increasing effluent concentrations reported during wastewater treatment attributed to solid-phase sorption upon entry into WWTPs and subsequent release into the liquid phase during secondary treatment (Verlicchi et al., 2012; Niemi et al., 2020). Clarithromycin has seasonably variable prescribing (monthly average ranging 6.10–11.22 g per person per day, and annual average of 74.2 g in 2022; SEPA, 2022), and high excretion fraction as the parent compound (average 38 % reported by Verlicchi and Zambello, 2016). This may increase the predicted mass loadings into the environment and predicted risk score in freshwater. For the current model, except for clarithromycin, it was observed that the PEC were below the PNECs (for approx. 50 % of catchments). However, the model adopts a precautionary approach assuming that all pharmaceuticals prescribed are taken as intended (i.e., excluding non-adherence, inappropriate disposal).

Overall, 8 catchments were shared across all four compounds with a higher probability of exceeding the risk score (>80 % risk level). These included the rivers (with local authority): Ore (Fife), Avon (Falkirk), Almond and Water of Leith (City of Edinburgh), Tweed (Scottish Borders), Kelvin (City of Glasgow), White Card Water (Renfrewshire) and Clyde (Lanarkshire). These catchments are located within, or bordering, the highly urbanised and densely populated “Central Belt”, representing approximately 70 % of the Scottish population (approx. 5.5 million) (National Records of Scotland, accessed 2023). As such, this region represents some of the most impacted catchments, based on population density, number and size of WWTPs and dilution profiles (i.e., smaller rivers receiving larger volumes of highly contaminated wastewater), and it is expected that mass loadings and risk would generally be highest here (Helwig et al., 2022). However, due to the upstream location of river level gauging stations, many urban centres were not included in the current version of the model. Several Scottish cities are located on the coast (e.g., Glasgow, Edinburgh, Dundee, Aberdeen), with receiving municipal WWTPs discharging directly to sea/estuaries. The GWFs for urban centres characterised by dense population and high prescribing activity were not captured in this version of the model. Future model refinement will aim to assess the GWF of these cities, and account for the prescribing data, WWTP influent and effluent data, and MEC data – however pharmaceutical pollution in estuarine/marine environments is lacking in Scotland (Helwig et al., 2022). Nonetheless, a hierarchy of risks from different substances per catchment was determined, with some rural catchments demonstrating higher risks for certain compounds.

Predicting pharmaceutical concentrations in the aquatic environment through drug usage data (i.e., prescription or wholesale data) has been performed across various regional/national scales in Sweden (Villén et al., 2023), Norway (Welch et al., 2023), Italy (Giunchi et al., 2023), Germany (Austin et al., 2021; Wöhler et al., 2020), the Netherlands (Wöhler et al., 2020), Spain (Austin et al., 2021), Croatia and Slovenia (Austin et al., 2021), and the UK (Austin et al., 2021; Jagadeesan et al., 2023). Modelling is a valuable tool for environmental prioritisation of contaminants at large scale, where there is limited or unavailable empirical data, or it is not feasible to collect data (i.e., due to site location, labour, costs). It can be useful to inform further investigations where potential risk was found to be high (Holm et al., 2013). In Scotland, comparison of pollution risk scores derived from MEC and PEC data indicated that the model generally overestimated risk, with MEC pollution risk scores demonstrating <10 % likelihood of exceeding the PNEC for the four compounds in selected catchments (90–99 % likelihood below the PNEC). Models are generally conservative by design, and overestimation of mass loadings and subsequent overprediction of environmental exposure has been reported elsewhere (Wöhler et al., 2020; Austin et al., 2021; Welch et al., 2023). This is likely due to a combination of factors, including limited observations representing some input factors (i.e., limited data on real WWTP removal rates, human excretion rates), and exclusion of important pathways by which pharmaceuticals may enter the environment (e.g., solid-phase sludge, combined-sewer overflows, direct disposal down sinks/toilets, over-the-counter sales, veterinary sources) (Kasprzyk-Hordern et al., 2021; Kay et al., 2017). Scotland has many private septic tanks (estimated 8 % of households, 170,000 properties) mainly located in rural areas, but the current register of septic tanks is incomplete (Scottish Government, 2022b). Thus, septic tank monitoring data is limited, and this may represent a significant unrepresented pathway for pharmaceuticals to reach the environment. Here, the PEC data is impacted by missing factors (e.g. solid-phase sorption, temporal variation, spatial resolution), and comparison with MEC data was limited low

sampling frequency in a specific catchment (i.e. one data point per month) (SEPA, 2022). Additionally, MEC data has inherently high variability, and some MEC surface water data was comparable to WWTP effluent concentrations, potentially due to WWTP proximity or unusually low river flows, however flow rate and environmental conditions are not recorded in the database (Helwig et al., 2022; SEPA, 2022). Future model improvements will include additional empirical data (e.g., site-specific WWTP drainage areas and treatment technologies) to refine model predictions at a finer geographical scale and temporal scale (i.e., using monthly rather than annual data to capture seasonality in river discharge, wastewater treatment, etc.). It will also capture and explore uncertainties in additional factors which could not be included due to data availability and resource limitations, such as different conceptualisations of the compound degradation in the environment.

4.3. General discussion

It was evident to environmental and healthcare stakeholders that mutual understanding is needed on how environmental aspects could be integrated into healthcare regulation and formulary development, and how this would affect the healthcare decision-makers in Scotland (i.e., SMC and ADTCs). In Scotland, the SMC acts as a single point advisory group for the HTA of newly licensed medicines which then guides local NHS Boards in formulary decision-making via ADTCs (Scottish, 2010; Scottish Medicines Consortium, 2018). Formularies are standardised lists of approved prescription medicines (at local, regional, national level), which promote high quality, evidence-based prescribing by rationalising the range and number of medicines considering clinical and cost-effectiveness (Alejandre et al., 2022; Scottish Medicines Consortium, 2018). Manufacturers provide data on the safety, efficacy and quality of pharmaceuticals when applying for marketing authorisation through the MHRA, while clinical and cost-effectiveness data is considered by the SMC when conducting HTAs on newly licensed medicines for NHS Scotland (Scottish Medicines Consortium, 2018). The SMC is composed of medical specialists, pharmacists, health economists, and representatives from NHS boards and the pharmaceutical industry and public (Alejandre et al., 2022). Ecotoxicologists and scientists with the expertise to assess and evaluate environmental risk and hazard data of pharmaceuticals are not included. From the workshop discussions, many from the environment sector were not aware of the process by which formulary decision-making and HTAs are performed, and which agencies are involved – although there was willingness to support with their expertise. This was similar from the clinical perspective, however there was more hesitancy in engaging with the environmental sector.

Improving the selection and use of the most environmentally harmful medicines may prevent degradation of key ecosystem services – while complementing wider healthcare initiatives addressing antimicrobial stewardship, and improving medicine adherence and appropriate disposal (Alejandre et al., 2022, 2023; Helwig et al., 2023; Moermond et al., 2023). However, standardised methods are lacking to enable critical comparison of clinical and environmental criteria in healthcare regulation (e.g., medical efficacy, safety, suitability, cost and environmental factors). Environmental risk assessments (ERAs) of human pharmaceuticals (products licensed post-2006) are undertaken by the EMA for product licensing prior to granting market access, following a 3-tiered approach including additional screening for persistence and bioaccumulation, where necessary (European Medicines Agency, n.d; Wess, 2021). However, where risk assessments may identify a potential risk, mechanisms are not in place to undertake a cost-benefit analysis comparing human health benefit to environmental risk – as current methods set human health benefit above environmental impact (Toolan et al., 2023; Moermond et al., 2023). Approaches were outlined which could facilitate inclusion of environmental information into healthcare decision-making, but standardised techniques are lacking to quantify impact across the full pharmaceutical lifecycle and different environmental domains (Toolan et al., 2023). Improvements could be instigated by incorporating available environmental information into existing HTA processes, such as/incentivising manufacturers to provide information about environmental costs or outcomes during procurement (Toolan et al., 2023). A framework was proposed for a universal standard to assess the environmental footprint of medicines across the "healthcare ecosystem", including carbon emissions, AMR, pharmaceuticals in the environment, packaging/plastics and green chemistry (BSI, 2022). Healthcare regulators could use this framework to consider environmental information related to the product chain (e.g., production, transportation, procurement, use/disposal), in addition to ecotoxicological information. However, it is likely that the current evidence gaps regarding pharmaceutical ERAs and risk-benefit analyses for incorporation of environmental information into standardised healthcare decision-making will require years of advocacy, collaboration, and consultation with healthcare professionals, patients, and the public before such breakthroughs will be a reality.

5. Conclusion

This proof-of-concept study demonstrates a novel, trans-disciplinary approach integrating public health, environmental science and qualitative health services methods and data to progress development of tools to introduce environmental data into healthcare decision-making in Scotland, focussing on pharmaceutical pollution in the water environment. The mixed methods study was delivered through consensus development techniques with stakeholders across the healthcare and environmental sectors, interrogation of environmental exposure and hazard data, and modelling and mapping to predict and visualise the environmental impact of selected pharmaceuticals in freshwater catchments. The framework was co-developed with stakeholders to predict the environmental impact of four pharmaceuticals of ecotoxicological concern in Scotland (clarithromycin, carbamazepine, fluoxetine, and propranolol) by generating individual pollution risk scores using the ratio of prescribed mass vs. mass that would not exceed the predicted no-effect concentration in the freshwater environment. A gradient of predicted risks were observed in freshwater catchments, with greatest risk observed in the most densely populated areas, and clarithromycin presenting the highest risk of the selected pharmaceuticals. Simulated risk scores were compared against observed risk calculated as the ratio of measured environmental concentrations (from national regulatory and research monitoring) and predicted no-effect concentrations. The model was observed to overpredict risk, and future work will refine the model by including additional compounds and sources (i.e., septic tanks, solid-phase transport, veterinary medicines), monthly variations to capture seasonality, and higher spatial representation (i.e., multiple sites within a catchment based on point-source proximity). The approach to modelling and visualising risk of pollution in the environment is generalisable, and the process outlined here can be adapted to other substances, media, and locations. The outputs have helped identify and progress methods for communicating complex environmental information to non-specialists in healthcare (Niemi et al., 2024 *in press*). However, it is evident that further collaborative and transdisciplinary efforts are needed to address the challenges regarding data availability, accessibility, and robustness. Bridging these knowledge gaps and facilitating meaningful engagement between the environment and healthcare sectors will be key to progressing environmentally informed prescribing and establishing more eco-directed healthcare practices in future.

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Ethics approval

This study was co-sponsored by NHS Highland and the University of Highlands and Islands. It was reviewed and given favourable opinion by NHS Research Ethics Committee (IRAS project ID 322050; REC reference number 22/EE/0307), the University of Nottingham Research Ethics Committee (REC reference number 005-2023), and the University of the Highlands and Islands Research Ethics Committee (REC reference number ETH2223-0075).

CRediT authorship contribution statement

Lydia Niemi: Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Naoko Arakawa:** Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Miriam Glendell:** Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Zisis Gagkas:** Writing – original draft, Visualization, Software, Methodology, Formal analysis. **Stuart Gibb:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Claire Anderson:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Sharon Pfleger:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary material to this article can be found online. Additional information about the UKRI MRC project is available at: https://ohbp.org/outputs/projects/developing-frameworks-for-eco-directed-sustainable-prescribing/. Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.176929.

Data availability

Data will be made available on request.

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