CREW CENTRE OF EXPERTISE FOR WATERS

Pharmaceuticals in the water environment: baseline assessment and recommendations

Main report

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Karin Helwig, Adeolu Aderemi, David Donnelly, Stuart Gibb, Lucyna Gozdzielewska, Jamie Harrower, Rachel Helliwell, Colin Hunter, Lydia Niemi, Eulyn Pagaling, Lesley Price, Joanne Roberts, Zulin Zhang

Hydro Nation International Centre

The James Hutton Institute

Scottish Government
Riaghaltas na h-Alba
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CREW CENTRE OF EXPERTISE FOR WATERS

Published by CREW – Scotland's Centre of Expertise for Waters. CREW connects research and policy, delivering objective and robust research and expert opinion to support the development and implementation of water policy in Scotland. CREW is a partnership between the James Hutton Institute and all Scottish Higher Education Institutes and Research Institutes supported by MASTS. The Centre is funded by the Scottish Government.

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Please reference this report as follows: Karin Helwig, Adeolu Aderemi, David Donnelly, Stuart Gibb, Lucyna Gozdzielewska, Jamie Harrower, Rachel Helliwell, Colin Hunter, Lydia Niemi, Eulyn Pagaling, Lesley Price, Joanne Roberts, Zulin Zhang (2022) Pharmaceuticals in the water environment – baseline assessment and recommendations. CRW2017/16. Available online with appendices at: www.crew.ac.uk/publications
CREW project managers: Nikki Dodd and Rachel Helliwell

ISBN: 978-0-902701-02-1

Dissemination status: Unrestricted

Acknowledgements: The project team wish to acknowledge the constructive input provided by the project steering group: Fiona Whyte, Lindsey Green, Dan Merckel, John Redshaw (SEPA), Elise Cartmell, Bess Homer (Scottish Water) and Sharon Pfleger (NHS Highland), and data contributions from the steering group and author organisations.

Cover photos courtesy of: Karin Helwig and Scottish Water

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Contents

List of Figures

List of Tables

List of Appendices

Glossary

AA	Annual Average
A&E	Accident and Emergency
AMIDS	Antimicrobial Management Integrated Database for Scotland
AMR	Antimicrobial resistance
BGS	British Geological Survey
BPA	Bisphenol A
BPS	Bisphenol S
CAS	Chemical Abstracts Service
CAS	Conventional Activated Sludge
CIP	Chemicals Investigation Programme
CRED	Criteria for Reporting and Evaluating Ecotoxicity Data
CREW	Centre of Expertise for Waters
DDD	Defined Daily Dose
EC	European Commission
EC50	Half Maximal Effective Concentration
ECOSAR	Ecological Structure-Activity Relationship
EDC	Endocrine Disrupting Compounds
EQS	Environmental Quality Standard
EMA	European Medicines Agency
ENV	Environment
ERI-UHI	Environmental Research Institute of the University of the Highlands and Islands
EU	European Union
GC-MS	Gas Chromatography-Mass Spectrometry
GCU	Glasgow Caledonian University
GIS	Geographical Information System
HEI	Higher Education Institutions
HMUD	Hospital Medicines Utilisation Database
ISD	Information Services Division (NHS)
LC50	Median Lethal Dose
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LOQ	Limit of Quantitation
LOD	Limit of Detection
MAC	Maximum Allowable Concentration
MDL	Minimum Detectable Limit
MEC	Measured Environmental Concentration
MIC	Minimum Inhibitory Concentration
MQL	Minimum Quantifiable Limit
NHS	National Health Service
NOEC	No-Effect Concentration
NSAID	Non-steroidal Anti-inflammatory Drug
NSS	National Services Scotland

NTIG	National Theatres Implementation Group
OHBP	One Health Breakthrough Partnership
PCA	Prescribing Cost Analysis
PEC	Predicted Environmental Concentration
PFI	Private Finance Initiative
PHS	Public Health Scotland
PIS	Prescribing Information System
PNEC	Predicted No-Effect Concentration
PPCP	Pharmaceuticals and Personal Care Products
PRISMS	Prescribing Information System for Scotland
QA	Quality Assurance
QC	Quality Control
QINRT	Quality Improvement National Reporting Tool
QSAR	Quantitative Structure-Activity Relationship
RIVM	Institute for Health and the Environment (the Netherlands)
RQ	Risk Quotient
RSD	Relative Standard Deviation
SAPG	Scottish Antimicrobial Prescribing Group
SEPA	Scottish Environment Protection Agency
SPARRA	Scottish Patients at Risk of Re-admission and Admission
SW	Scottish Water
TF	Trickling Filter
UHI	University of the Highlands and Islands
UKWIR	UK Water Industry Research
WL	Watch List
WWTW	Wastewater Treatment Works
WFD	Water Framework Directive

Executive Summary

Research questions

The project had the following objectives:

1. To assess the spatial and temporal availability of baseline data in Scotland and to identify gaps in the available datasets, including any quality concerns, by collecting, collating, reviewing and processing monitoring data from the One Health Breakthrough Partnership (OHBP) organisations, from the scientific literature, and as far as possible from other data holders such as Universities.
2. To identify threshold values for ecotoxicity and selection for antimicrobial resistance (AMR) (where appropriate) and to evaluate environmental concentrations of pharmaceuticals against these.
3. To conduct a gap analysis and to make recommendations for small-scale gap filling.
4. To provide initial recommendations on visualising the baseline dataset and related information based on the findings of objectives 1 and 2.

Background

Following consumption by patients, pharmaceuticals and their metabolites are excreted into the sewer and reach wastewater treatment works (WWTW), which are unable to fully remove them. Advanced treatment technologies are available but are cost- and energy intensive. Source control could play a key part in the reduction of risk from pharmaceutical substances, for example by taking environmental information into account in prescribing decisions. Whilst various prioritisations have been produced internationally, risk depends on local consumption, wastewater treatment infrastructure, and condition of the receiving environment (e.g. dilution). This project sought to establish an environmental baseline to inform changes to prescribing in Scotland and to enable future assessment of effectiveness of measures against this baseline.

Research undertaken

This project brought together data from a range of sources to establish the availability of baseline information on the occurrence of pharmaceuticals in the aquatic environment. Mean concentrations for each monitored location were assessed against threshold values for environmental (ecotoxicological) risk and, for antibiotics, against threshold values above which the substance might act a driver for AMR. The project also sought to identify datasets relating to the prescription data of these pharmaceuticals, and to provide recommendations on gaps in the baseline and initial recommendations on visualising the dataset. The scope of the project was restricted to data pertaining to Scotland relating to monitoring projects undertaken between 2014 and 2019. Although pharmaceutical substances, or substances and their metabolites, can have cumulative effects, the risks calculated in this project are for single substances only, in line with the current regulatory regime on Environmental Quality Standards.

It should be noted that about half of the monitoring data collected refer to samples targeting high-risk settings, such as immediately downstream from a WWTW, and are thus not representative of 'typical' environmental concentrations in the water body. Regulatory (WFD) sampling points are chosen to be representative of water quality in the water body.

Key findings

- **Data were compiled on 60 substances in 11 distinct environmental matrices[1], into a project database of 3074 data points representing unique substance-location-data source combinations.**
  It should be noted that as the studies used different methods, concentration data are not directly comparable. For some studies, it is important to pay attention to not only the concentrations but also the detection frequency, due to differences in data handling. Database entries should therefore be considered with reference to this report, which gives detail on the particular conditions pertaining to each study.
- **Thresholds for ecotoxicological effects and AMR (where applicable) were found for the majority of substances**.
  Ecotoxicological thresholds were found for 51 substances, although not all of these have the same level of robustness. AMR thresholds were found for all antibiotic substances; these are all taken from the same publication and are thus comparable, but it should be noted that this is a relatively new type of risk assessment and further work to validate the proposed thresholds is required.
- **In terms of ecotoxicological risk, a total of eight substances were identified as posing a higher risk in Scottish waters, five of which were taken forward in a mapping exercise for visualisation purposes.**
  Ibuprofen, clarithromycin, erythromycin, diclofenac, EE2, metformin, ranitidine, and propranolol were

1 Environmental matrices i.e. surface water (river or stream, loch, estuary), WWTW media (influent, effluent, primary and secondary), septic tank effluent, hospital sewage (untreated) and mains drinking water. See Section 3.3.3.

identified as posing a higher risk, based on a holistic consideration of risk quotients, detection frequency, and prescription volume. Bearing in mind that several studies deliberately sought to sample in high-risk (low dilution) locations, in total, 217 data points indicated ecotoxicological risks (mean Risk Quotient (RQ) > 1), of which 47 indicated very high risk (mean RQ > 10). For the majority of compounds in the database, environmental risks are low at all or most locations.

- **Three substances were identified as posing a higher risk in terms of AMR. Two of these overlapped with the ecotoxicological higher-risk substances. AMR risk was visualised in maps for all three.**
  These substances are clarithromycin, erythromycin, and ciprofloxacin. With the exception of a few locations only, antibiotic residues in surface water were below the threshold where they might drive selection for resistance. Based on the current evidence, pharmaceutical residues in surface waters therefore do not appear to pose a major risk in terms of driving selection for antimicrobial resistance and the highest risks are posed by antibiotics that are already monitored by SEPA. However, for all three of the highlighted antibiotics, concentrations in WWTW commonly exceeded these concentrations; over 100 datapoints indicated a risk of driving selection for AMR.

- **A gap analysis revealed that there are knowledge gaps in terms of compounds analysed, spatial representation, and in relation to some possible point sources.**
  The substances in the project were screened against three existing priority lists; for 18 compounds on these combined lists no monitoring data was found. Spatial analysis of the project database revealed that substantial gaps also exist in terms of geographical area, with no data at all for 18 Local Authority areas. Surface water measurements are mostly in rivers and burns, with only a few data points available for loch and estuarine water bodies and none at all for coastal waters or groundwater. Only 24 out of Scotland's 391 catchments have been sampled, although these may well include the most impacted catchments due to the risk-based approach of some of the studies. Whilst a significant amount of data was available for WWTW influents and effluents (from Scottish Water's extensive Chemicals Investigations Project 2 Scotland), little data was found on septic tanks and none on other potential sources such as agricultural, aquaculture, landfill or manufacturing discharges. Whilst the PILLS project (https://keep.eu/projects/7018/) investigated hospital effluents in 2012, data was too old to include in the project database and only one of the studies included investigated hospital effluent.

Recommendations

With reference to our objectives, it is recommended that:

- Gaps in the dataset are addressed by targeting a number of substances that have never been monitored in Scotland (possibly following screening against consumption); by undertaking risk-based sampling in geographical areas where no data is available; by sampling of groundwater, lochs, coastal waters and estuarine waters; and by sampling in proximity to sources for which little data exists.
- The PNEC database is expanded and consolidated through in-depth analysis of available toxicity data to ensure robustness of the calculated risks, in line with the objective for filling remaining knowledge gaps adopted in the EU's Strategic Approach to Pharmaceuticals in the Environment, including for substances considered as alternatives for higher-risk pharmaceuticals, in order to avoid "regrettable substitutions".
- A range of visualisations, including an interactive Geographical Information System (GIS) map, is considered to communicate information on pharmaceutical risk to different audiences.

Furthermore, based on insights gained during the research process, it is recommended that:

- The presence of antimicrobial-resistant genes in and downstream from WWTW is investigated.
- The project database is maintained as a permanent, secure, shared database, using the change tracker provided to enable longer-term monitoring and management of pharmaceutical concentrations in the environment, and that a database custodian is appointed.
- A review is undertaken of existing modelling approaches to predicting environmental pharmaceutical concentrations with a view to adopting one in Scotland, exploring the possibility of utilising NHS consumption data and Scottish Water data on sewer and WWTW infrastructure.
- Any intervention for the reduction of pharmaceuticals in Scottish surface waters is embedded in a comprehensive strategy, which would need to be developed.

1.0 Introduction

1.1 Background and scope

Pharmaceutical substances in the water environment can be persistent, ecotoxic, bio-accumulate, and contribute to the introduction or proliferation of anti-microbial resistant bacteria and other microorganisms in the environment. The waste streams containing these pharmaceutical compounds originate from many sources, including veterinary sources, but are thought to enter the environment predominantly as a result of human excretion via WWTW. Wastewater treatment works are unable to fully remove all pharmaceuticals and their metabolites. For commonly used medicines, domestic use is widely recognised as the overall greatest source but for some specialist medicines, hospital use can lead to 'hotspots' (Kümmerer, 2001; Helwig et al., 2016). Increased wastewater treatment alone is not a sustainable method to keep pharmaceutical compounds from entering the water environment, as this can be cost- and carbon-intensive. Source control is therefore a key part of the solution to protecting the water environment.

The concept of "Essential Medicines" (World Health Organisation, 2019) introduced by the World Health Organisation in the 1970s, provided a list of medicines that were selected based on safety, clinical effectiveness, and cost effectiveness. This idea has been widely adopted across the world with local health systems developing their own formularies (a list of medicines recommended for prescribing). Stockholm County Council has widened the selection criteria for formulary choice to include environmental considerations and published the Wise List (Janusinfo, 2018). Where clinical and cost-effectiveness of medicines are equal, then the environmental impact of the medicines is considered to decide which should be the preferred choice of medicine to prescribe. Updating local formularies in this manner to promote more prudent environmental prescribing choices potentially reduces negative impacts of pharmaceuticals and their metabolites on the water environment.

Performing similar formulary updates across Scotland requires an understanding of what pharmaceuticals are currently of concern in Scotland, as well as developing a method to link this new information into the existing NHS prescribing system and inform prescribers and patients of the changes. The One Health Breakthrough Partnership[2] (OHBP) plans to pilot an updated version of the NHS Highland formulary that will incorporate environmental effects. Prior to making any changes to existing Scottish NHS formularies, this study sought to establish baseline monitoring data against which the impact of the envisaged changes in prescribing can be assessed.

As changes to formularies are made regularly for other reasons – e.g. for clinical reasons, new medicines coming to market or concerns about antimicrobial resistance (AMR) - and hospital and wastewater infrastructure also develop over time, the project only considered results from studies that finished sampling in or after 2014. Including older studies could focus attention on drugs that are no longer relevant, on discharges from hospitals that no longer exist, or on sites where upgrades to treatment systems have since taken place, or indeed could have lowered mean concentrations for drugs for which consumption is increasing.

1.2 Project objectives

The overall aims of this project were to assess the availability of baseline information for both existing water monitoring data and also for prescription data for these pharmaceuticals, and to provide recommendations on gaps in the baseline dataset and initial recommendations on visualising the dataset.

The project had the following objectives:

1. To assess the spatial and temporal availability of baseline data in Scotland and to identify gaps in the datasets (including any quality concerns) by collecting, collating, reviewing and processing monitoring data from OHBP partner organisations, from the scientific literature, and as far as possible from other data holders such as Universities;
2. To identify threshold values for ecotoxicity and selection for AMR (where appropriate) and to evaluate environmental concentrations of pharmaceuticals against these.
3. To conduct a gap analysis and to make recommendations for small-scale gap filling.
4. To provide initial recommendation on visualising the baseline dataset and related information based on the findings of objectives 1 and 2.

1.3 Outline of the report

Section 2 of this report describes our research, beginning with the identification of relevant datasets (2.1), through a three-pronged approach: in first instance through literature search for studies on pharmaceuticals in the Scottish environment; secondly, through our network

2 The One Health Breakthrough Partnership consists of five core organisations (NHS Highland, University of Highlands and Islands - Environmental Research Institute, SEPA, Scottish Water, Highlands and Islands Enterprise) and nine partner organisations (CREW, James Hutton Institute, Talking Medicines, Forrit (previously Cortex Worldwide), Healthcare Without Harm, Glasgow Caledonian University, Glasgow University, Strathclyde University, Edinburgh University).

at Scottish Higher Education Institutions and research institutes; and thirdly, by identifying and collating datasets held by the OHBP partner organisations. Next, we describe our approach to screening (2.2) and data extraction (2.3). In section 2.4, we report on identifying threshold concentrations and our approach to risk assessment. Section 2.5 describes the approach to gap analysis, section 2.6 describes quality assurance and control and finally section 2.7 the mapping method.

Section 3 reports on our findings, starting with an overview and characterisation of the studies included (3.1) and highlights compounds of particular concern (3.2) either because of risk to aquatic organisms or because the threshold for driving selection for antimicrobial resistance were found to be exceeded, to arrive at an overall prioritisation of the pharmaceuticals considered. Following on from this we present the results of the gap analysis (3.3). A description of the available datasets relating to prescribing follows (3.4).

Section 4 presents a discussion on the findings and section 5 our recommendations.

2 .0 Research undertaken

2.1 Identification of datasets

A three-pronged approach was undertaken to identify relevant datasets: a literature review, a network approach, and a selection of the OHBP partners' own data.

2.1.1 Literature review

A literature review was undertaken to identify any studies within the scope of the project (pertaining to environmental measurements of pharmaceuticals in Scotland with (sampling) dates restricted to 2014 to the present. PhD theses were searched via the British Library's EThOS service and through our network of academic contacts. Findings are described in 3.1.

As none of the studies identified pertained to groundwater, publications of the British Geological Survey (BGS) were searched specifically on this topic. A 2011 Report "Emerging Contaminants in Groundwater" (BGS, 2011) was available but did not contain any data

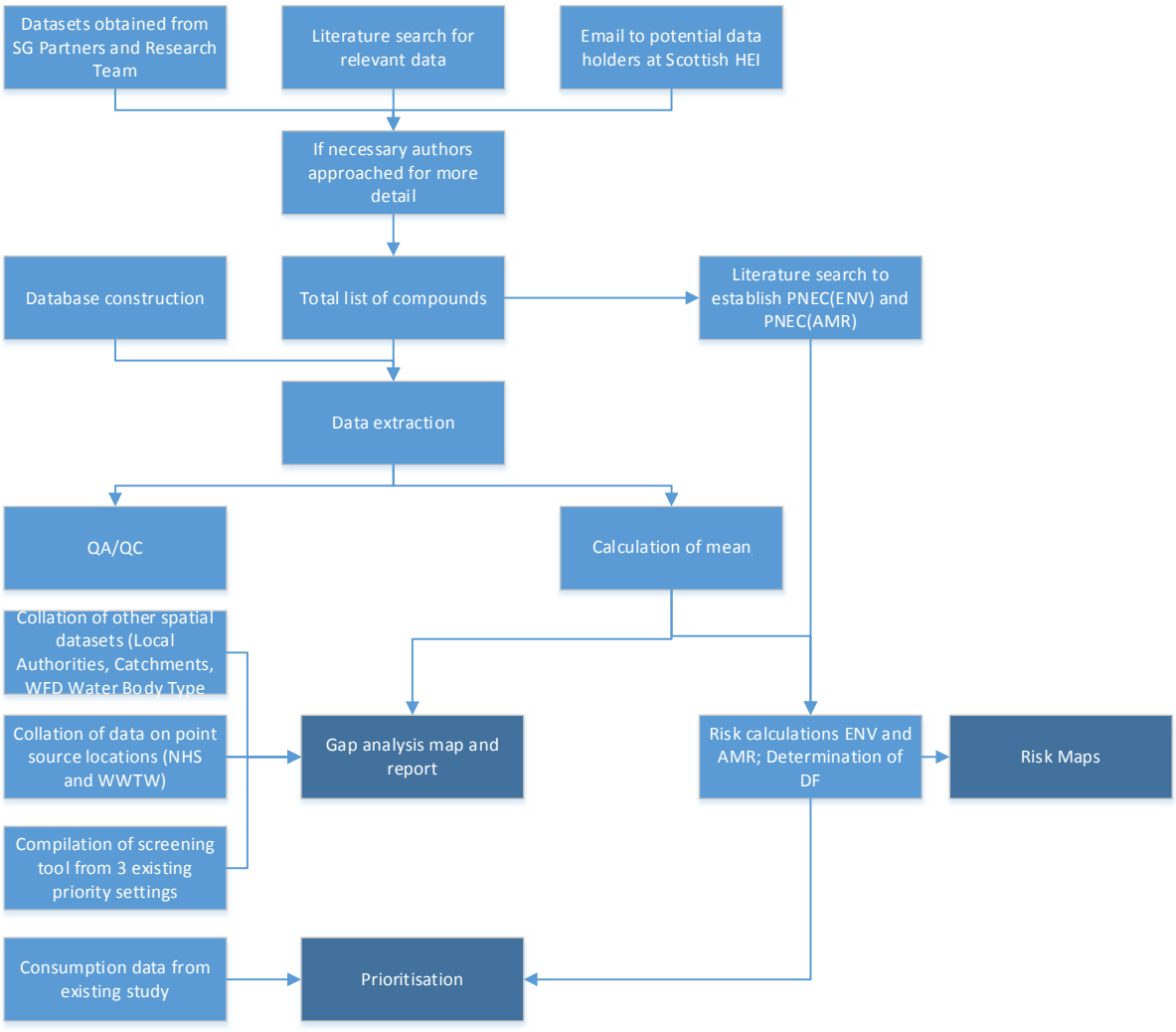

Figure 1 Project Approach. SG refers to CREW project Steering Group.

pertaining to Scotland and was in any case too old for any data to be included.

The Scottish Pollutant Release Inventory (https://www.sepa.org.uk/environment/environmental-data/spri/) was also consulted but yielded no pharmaceutical results post-2014.

2.1.2 Network approach

The research team made contact with colleagues at Scottish Higher Education Institutions with a request for any relevant data or for any information on projects they might be aware of.

2.1.3 Partner datasets

All partners involved in the project – The James Hutton Institute, the Environmental Research Institute at the University of the Highlands and Islands and Glasgow Caledonian University - have conducted multiple environmental monitoring projects on pharmaceuticals. The Scottish Environment Protection Agency (SEPA) and Scottish Water (SW) also hold significant datasets. All data pertaining to sampling periods from 2014 to the present were included.

2.2 Selection of compounds for inclusion

The initial scope in terms of compounds, or the 'long list' for the project, comprised of two priority settings:

- The list of 25 drugs identified as 'Environmentally Harmful' by the Stockholm Region (https://janusinfo.se/downnload/18.5f0ead9216532d0a6a113e1f/1549524964351/Forteckning-over-miljobelastande-lakemedel.pdf; Appendix I).
- The UK Water Industry Research (UKWIR)'s Risk-based prioritisation of pharmaceuticals (Boxall et al. 2014)

As the UKWIR list was based on the whole of the UK and did not include the use of medicines in hospitals, and the list of 25 Environmentally Harmful drugs is based on regional data on environmental risk for Stockholm, a third priority list was added by the research team to ensure relevance for the Scottish context:

- The top 20 list of pharmaceuticals by environmental risk as identified by Helwig et al. (2016).

The compounds identified in these three studies were used as a first screen to determine the 'long list' of pharmaceuticals considered.

However, as most studies only reported on a limited number of compounds, any other compounds investigated in the studies were also included in our database if it was not too onerous to do so, in order to build a more comprehensive picture. This was possible for all datasets apart from the SEPA dataset, which contained a much larger range of compounds.

In total, the project database contains data for 60 substances (Appendix II).

2.3 Approach to data extraction, collation and processing

2.3.1 Data extraction

To present data collated from heterogeneous sources in a meaningful way is challenging. As different research projects and monitoring programmes have different objectives and use different methods both for sampling, analysis and for data processing, results are not directly comparable. Nevertheless, it can be useful to bring datasets together to identify overall patterns and gaps. Our approach was loosely based on that adopted by Aus der Beek *et al.* (2015), who, in an extensive review of the literature, collated data on measured environmental concentrations of pharmaceuticals from over 1000 publications from around the world.

In our study, each dataset was allocated a reference number (in no particular order), which allows a brief characterisation of the details of the study to be readily accessed to aid interpretation of specific values. For example, noPILLS sampling was undertaken during a low flow period in summer, so that the mean concentration values from this study are potentially elevated compared to other studies. An overview of the studies and their characterisations are given in section 3.1.

Data were abstracted on five main aspects: substance, location, sampling detail, laboratory processes and analysis, and results as follows:

Pharmaceutical substance: its name, Chemical Abstracts Service number, and therapeutic class.

Location: the environmental matrix the substance was measured in, geographical location, and location description.

Sampling detail: sampling method (grab, automated or passive sampling), any additional sampling detail, year, start and end date of the sampling period, and the number of measurements.

Laboratory processes and analysis: the sample storage method, the extraction method, the instrumental analytical method, analytical method with detection limit

of the analytical method employed, calibration details, recovery, analytical variability, whether the laboratory was ISO-accredited, and Limit of Quantitation (LOQ) or Limit of Detection (LOD) (see section 2.5);

Results: the number of positive detections, uptake rate (for passive sampling), mean measured concentration in original and standardized units, details of how the mean was calculated.

2.3.2 Data collation

A few points should be noted with regard to data collation:

- Drug names were harmonised (e.g. acetaminophen was changed to paracetamol; E2, 17-beta oestradiol, 17-β oestradiol, 17-beta estradiol and 17-β estradiol were all changed to 17-beta oestradiol (E2), etc.).
- Where metadata was not included by the authors, but it was possible to add this with reasonable certainty it was included by the team (e.g. Chemical Abstracts Service (CAS) numbers or therapeutic class).
- In indicating the therapeutic group, broad groups were used (e.g. antihypertensive rather than beta-blocker).

2.3.3 Data processing

Data processing was limited to calculation of the mean concentration found in the study (where none was given by the author) and the Relative Standard Deviation (RSD).

Determination of environmental concentrations and their means

Generally, we have adopted the author's or data holder's preference on how data are reported and processed. This pertains in particular to two issues: analytical recoveries and calculation of the mean.

In analytical chemistry, the recovery of a substance is experimentally determined. Recovery experiments with spiked samples are conducted; if the concentration found is between 80% and 120% this is considered acceptable. In most cases, the concentrations of the pharmaceuticals in the matrix are then reported as found, i.e. there is no correction step to compensate for the recovery value. There is one exception to this in this project: Letsinger et al. (2019) did correct for recoveries.

There is no single accepted way to calculate the mean for environmental data. Some have proposed using ½ LOD or ½ LOQ, but as a normal distribution is not expected in pollutant concentrations, this is somewhat arbitrary. Others prefer to report the mean of the quantifiable positive detections only, which should then be considered alongside the number of positive detections as a fraction of the total number of samples. Details are provided in the data source descriptions in section 3.1.

Non-quantifiable risk

For some substances and locations, risks could not be quantified either because no PNEC was available or because all measurements were below the limit of detection. Entries in the original datasets were included < MQL – Minimum quantifiable limit, NA - Not applicable, ND – Not detected, < LOQ, < LOD, < MDL - Minimum Detectable Limit. The Risk Quotient for a concentration below the limit of quantitation is not zero, but non-quantitative values cannot be mapped in ArcGIS. We still wanted to include these datapoints in the database, to indicate that sampling was undertaken. Therefore, artificial values were substituted in the database (Table 1).

Table 1 Artificial values substituted into project database

Original table value	Updated table value
<MQL	-994
NA	-995
ND	-996
<LOQ	-997
<MDL	-998
Blanks	-999
- (minus or dash)	-993

A note on Relative Standard Deviation

It should be noted that the calculation of a Relative Standard Deviation (RSD) in environmental concentrations is statistically questionable, as a normal distribution cannot be assumed. Nevertheless, the calculated RSD gives some idea of the spread of the concentration values and is included in the spreadsheet.

2.4 Quantification of risk

The accepted method to calculate the potential environmental risk of a pharmaceutical, or any chemical, is based on the determination of the concentration of a compound expected in the environment, or Predicted Environmental Concentrations (PECs), and the concentration below which no effects are expected, or Predicted No-Effect Concentrations (PNECs) and expressing their association as a ratio or Risk Quotient (RQ):

$$RQ = \frac{PEC}{PNEC} \qquad \text{(Equation 1)}$$

Where Measured Environmental Concentrations (MEC) are available, risk can also be defined as:

$$RQ = \frac{MEC}{PNEC} \quad \text{(Equation 2)}$$

In the European Water Framework Directive, Environmental Quality Standards (EQS) are set based on this kind of risk assessment, whereby two distinct limits are set:

- a threshold for the average concentration of the substance concerned, calculated from measurements over a 1-year period (annual average (AA)). The purpose of this standard is to ensure protection against long-term exposure to pollutants in the aquatic environment.
- a maximum allowable concentration (MAC) of the substance concerned, i.e. the maximum for any single measurement. The purpose of this standard is to ensure protection against short-term exposure, i.e. pollution peaks (Directive 2008/105/EC).

The two main reasons why pharmaceutical residues in the environment give cause for concern are toxicological effects on aquatic organisms and the potential to act as a selective driver for the maintenance and / or occurrence of antimicrobial-resistant genes, particularly antibiotics. To quantify risk from a pharmaceutical compound in terms of both of these contexts therefore requires comparison with two separate threshold values, one for environmental risk - PNEC(ecotox) - and one for the risk of driving AMR - PNEC(AMR).

In this project, only risks based on measured environmental concentrations were quantified so the two risk quantifications were calculated as follows:

$$RQ(ENV) = \frac{MEC}{PNEC(Ecotox)} \quad \text{(Equation 3)}$$

and

$$RQ(AMR) = \frac{MEC}{PNEC(AMR)} \quad \text{(Equation 4)}$$

A similar approach was adopted by the AMR Industry Alliance Antibiotic Discharge Targets (Tell et al., 2019).

Using MEC rather than PEC is a particular strength of this study. The PEC is a prediction of the expected concentration in the environment based on total consumption and both in-sewer and environmental dilution, sometimes refined by metabolic characteristics (e.g. the percentage excreted as parent compound) or removal efficiency in wastewater treatment processes (e.g. Helwig et al., 2016). Metabolism of pharmaceuticals vary among humans with age, sex and frailty (McLachlan and Pont, 2011) all affecting the pharmacokinetics and thus excretion. The removal process, in the case of pharmaceuticals, mainly occurs at the WWTW, but could involve natural processes such as photo-degradation or absorption onto sludge or soil particles. There is no standard construction for WWTW, and the time material remains within the WWTW varies, as does the composition of the raw influent, so the percentage removal value for a drug can differ between studies. Verlicchi et al. (2012), in their review of pharmaceutical removal from urban wastewater, reported that for diclofenac, for example, the removal rate ranged between 3 and 65.1% in the 18 studies they reviewed. Removal also varies significantly between drugs (ibid.). Additionally, many pharmaceuticals, due to their usage, are not continuously released into the sewage system and with variations based on season or population age. Thus, quantifying the PEC of a pharmaceutical relies on a number of assumptions that can influence the final value and the actual concentration in the environment is likely to vary considerably not only spatially but also temporally.

An advantage of PEC studies, however, is that a more systematic and comprehensive approach can be adopted to the inclusion of compounds in the risk analysis. Many compounds have never been measured in the environment simply because nobody has looked for them, as most chemical analysis uses methods targeted to the quantification of specific compounds. Some would also argue that the use of PEC values protects against the possibility of active metabolites, which may be toxic but are rarely analysed separately. Predictive risk assessment, using PECs, is common practice in marketing and use regulations to ensure the safe use of chemicals.

The gap analysis made use of a prior study involving PEC calculations (Helwig et al., 2016) that used Scottish consumption data to predict environmental risk; this study only considered ecotoxicological risk but as antibiotics tend to have low PNEC(ecotox) values it still provides some robustness in terms of gap analysis of a compound's potential to drive AMR.

More complex methods for quantifying risk are available, for example those involving exposure calculations or fish plasma concentrations (Burns et al., 2018), but these were beyond the scope of the project.

2.4.1 Environmental risk thresholds

Although PNEC(ecotox) can be derived for a range of habitats or fauna, unless specified otherwise $PNEC_{fresh\ water}$ is implied. Toxicity in sediment organisms has not been considered since retrieved data refer to water column concentrations.

PNECs are generally based on laboratory-based ecotoxicity experiments for a range of endpoints, whereby a single species is exposed to a single drug. Most commonly, endpoints include growth, reproduction or mortality. Data are typically reported as the concentrations where either a percentage reduction of the parameter was observed,

typically either 50% inhibition of growth or mortality (EC50 or LC50; Median Effective Concentration /Median Lethal Concentration), or – preferably - as No Observed Effect Concentration (NOEC), where NOEC is the highest concentration tested with no statistically significant difference in effect compared to the control. In preference, values should be obtained from long-term (chronic) eco-toxicity studies, which extend over multiple generations of the test organism. The accepted base-set of organisms for deriving $PNEC_{fresh\ water}$ comprises of algae, *Daphnia* and fish, representing three trophic levels: algae as primary producers; *Daphnia* as primary consumers and fish as secondary consumers (European Commission, 2018). The result from the most sensitive species being used in the risk evaluation.

To calculate the PNEC, an Assessment Factor is then applied, which can range from 10 to 1000. This is included as a protective factor to allow the transfer of laboratory results to real ecosystems, for the fact that the laboratory evaluation does not include the entire range of organisms present in these situations and for the fact that other stressors will be present. The more extensive the experimental ecotoxicity data available, the smaller the Assessment Factor (Table 2).

In this project, in order to determine environmental (ecotoxicological) risk, a search for PNEC(Ecotox) values was based on the available literature. For some compounds, following communication with the Project Steering Group, data previously adopted by the Steering Group partners (e.g. in the CIP2 Scotland project) was used. PNEC values were found for nearly all substances, but one study (Ramage et al. 2019) was included in the project after the PNEC literature search had already been completed. Therefore, PNEC data for any substances that were only analysed in this study is not included and RQ values were not calculated for the results in Ramage et al. (2019). Where available, the Assessment Factor is indicated in the spreadsheet in order to give an indication of the robustness of the PNEC value; this information was however not available for the substances whose values were taken from the CIP2 Scotland project. Substances with high assessment factors have also been highlighted in the gap analysis.

All PNEC values adopted in the project and their references are included in Appendix VII.

2.4.2 Antimicrobial resistance risk

Minimum selective concentrations

While environmental AMR has been a cause of concern for some time, this has not yet led to regulatory controls on antibiotic residues in the environment, although several are on the Watch list. Bengtsson-Palme and Larsson (2016) first proposed regulatory limits for antibiotic drugs based on Minimum Inhibitory Concentrations (MIC), quantifying upper boundaries for selective concentrations for 111 antibiotics and predicting no-effect concentrations for resistance selection, based on the assumption that selective concentrations *a priori* need to be lower than those completely inhibiting growth (Bengtsson-Palme and Larsson, 2016). The proposed PNECs are based on the lowest observed Minimal Inhibitory Concentrations (MIC) with an Assessment Factor of 10 and range from 8 ngL^{-1} to 64 μgL^{-1}. In most cases, these PNECs were below the available PNECs for ecotoxicological effects, implying that for antibiotics, the AMR threshold tends to be more sensitive. The values used for PNEC(AMR) in this project were taken directly from this publication and are included in Appendix VII.

Antibacterial effects for non-antibiotics

Non-antibiotic drugs can nevertheless have antibacterial effects and when this is the case they can potentially contribute to the development of proliferation of AMR. A mini-literature review was undertaken to establish for which drugs this may apply. MEDLINE was searched on the 27th August 2019 for records on antibacterial effects of non-antibiotic drugs of interest. MEDLINE database was chosen because it contains a large number of peer-reviewed journals from around the world, covering a broad range of biomedical and health topics. A mixture of MeSH terms and free text words, including the generic name, compound name and brand names of each drug were combined. The full results of literature review are provided in Appendix VIII. Some gaps remaining after the MEDLINE review were supplemented by further targeted review.

Table 2 Assessment factors used to derive a PNEC(freshwater) (European Commission, 2018)

Available data	Assessment factor
At least one short-term L(E)C50 from each of three trophic levels (fish, Daphnia and algae)	1000
One long-term EC10 or NOEC (either fish or Daphnia)	100
Two long-term results (e.g. EC10 or NOECs) from two trophic levels (fish and/or Daphnia and/or algae)	50
Long-term results (e.g. EC10 or NOECs) from the three species (normally fish, Daphnia and algae) representing three trophic levels	10

2.5 Gap analysis

The gap analysis was primarily performed through mapping and visualising of the project database, which included 3,073 datapoints (Appendix III).

This analysis comprised three main foci. Firstly, a critical review of this database was undertaken to identify relationships between pharmaceutical monitoring locations and other spatial data, specifically Scottish Local Authority area, river catchment, and point source proximity (i.e. whether sites likely to be affected by NHS centres and WWTWs were included). In this exercise, database entries were classified by environmental matrix. Summary statistics and plots were produced with R statistical software (R version 3.6.0) and Microsoft Excel (version 2016).

Consideration was also given to compounds on priority lists for which environmental monitoring data is lacking in Scotland, using again the Stockholm list of Environmentally Harmful Pharmaceuticals, the UKWIR prioritisation by Boxall et al. (2014) and the consumption-based analysis by Helwig et al. (2016).

2.6 Quality assurance and control

2.6.1 Quality of environmental measurement data

Many different laboratories were involved, some directly and some contracted by data providers, and each of them has their own analytical method and quality control. However, as expected, a number of common protocols were employed for the various monitoring studies. Therefore, here we summarize the most commonly used sampling, extraction, instrumental analytical methods and quality control procedures for the collected data.

Sampling, Extraction and Instrumental Method

Spot(grab) sampling was employed by all data providers. Normally, water samples (e.g. 500 mL or 1 L) were collected and a procedure blank would also be prepared along with the sampling campaign. In some studies, a biocide (e.g. sodium azide) or hydrochloric acid/copper nitrate was added into each sample to eliminate bacteria and prevent sample degradation during storage and processing. In all studies, the samples were stored in cold conditions (e.g. refrigerated below 4° C) until further preparation and analysis. Subsequently, the water samples were filtered under vacuum through pre-ashed glass-fibre filters (e.g. GF/F, 0.7 µm) and the target compounds were extracted from filtrates by using the Solid Phase Extraction cartridge (e.g. Oasis HLB or Strata-X). Briefly, all the cartridges were first conditioned by organic solvents (e.g. methanol) and then ultrapure water. Following this, water samples were loaded and extracted (e.g. at a flow rate of 5-10 ml/min). After the extraction, the cartridges were dried (e.g. under vacuum for 30 min) and the analytes were eluted into glass vials from the sorbents with organic solvents (e.g. methanol: acetonitrile). The extracts were analysed by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) (e.g. triple quadrupole mass spectrometry) or were subjected to derivatisation followed by Gas Chromatography-Mass Spectrometry (GC-MS) analysis.

Quality Control

No single approach to Quality Control (QC) has been defined, owing to different practices in the different laboratories involved. However, in general, the QC programme is expected to include the following features. Relevant standards would be analysed to check instrumental performance (e.g. peak height/area and resolution) prior to the real sample analysis. Quality Control samples would be determined in each batch of analysis. For example, procedural blanks would be run to check the control of contamination. Reference standard mixtures (calibration standards) would be run for the peak identification and instrumental quantification (e.g. compounds were identified mainly by monitoring ion and by their retention times). Standard calibration curves would be tested for linearity (through correlation coefficient, $r^2 > 0.99$ for good linearity). A similar contamination level to the real samples is spiked and tested for the recovery estimation in each batch of samples, and the reproducibility of the method is monitored by repeated analysis of spiked samples. The LOD would be defined as the concentration that corresponds to three times the standard deviation of blanks, is measured by integrating peak area for each analyte in 10 independent blanks (e.g. ultrapure water). The LOQ is the lowest contaminant concentration that can be quantified in a sample with acceptable precision under the stated operational conditions of the method. LOQ is determined as the analyte concentration corresponding to a signal/noise ratio of 10. Overall, the LODs for different compounds were in the range of sub-parts per trillion level to parts per billion.

2.6.2 Adequacy of the PNEC data

PNEC(AMR)

PNEC(AMR) data is taken from a single publication, authored by the highly respected Johan Bengtsson-Palme and D.G. Joakim Larsson (Bengtsson-Palme and Larsson, 2016). The latter is also involved in selecting hazard and risk information for the Swedish WISE-list project. Several authors have utilised this dataset in the same way as has been done in this project (e.g. Singer et al., 2019; Tell et al.,2019). Nevertheless, this is a relatively new approach

and not yet empirically validated in the water environment as far as we are aware.

It is well known that the presence of non-antibiotic compounds, including for example heavy metals or other pharmaceuticals, can also lead to increased proliferation of antimicrobial resistant genes (ARG). PNEC(AMR) was only quantified for antibiotics.

PNEC(Ecotox)

Given that the eco-toxicological parameter from the most sensitive species is used in the risk assessment or even, in the case of multiple NOEC's or EC50's, the lowest value (relating to the most sensitive end point) from one species, ensuring that the data is reliable, relevant and adequate is paramount. Adequacy, as defined in the European Chemicals Agency's Technical Guidance Document on Risk Assessment, comprises two elements:

- reliability: covering the inherent quality of a test methodology and the way that the performance and results of the test are described.
- relevance: covering the extent to which a test is appropriate for a particular hazard or risk assessment (European Commission, 2018).

Relevance refers, *inter alia*, to appropriate end points and test conditions. Various methods exist to assess reliability, notably the Klimisch scoring approach (Klimisch et al., 1997) and the more recent "*Criteria for Reporting and Evaluating Ecotoxicity Data (CRED)*" method (Kase et al., 2016). In this project, resources did not allow for detailed review of ecotoxicology studies and, importantly, the robustness of the reported risk values must be considered low until PNEC data have been fully assessed for reliability. A more detailed consideration of confidence in PNEC values is given in Appendix IX.

2.7 Mapping and visualisation

The data collated through activity 2.3.2 *Data collation* was used to produce a table of 3,073 records in Excel format, representing unique substance-location combinations. This data was the input for mapping and visualisation. The data included spatial coordinates in a range of types, and these were reformatted and where necessary re-projected into Ordnance Survey easting and northing coordinates. The data was formatted to enable it to be imported into the Geographic Information System ArcGIS Pro (v2.4.0) where all subsequent mapping activity took place.

Additional data in the mapping consisted of SEPA catchments, downloaded from SEPA's environmental data portal; Waste Water Treatment Works supplied by Scottish Water; NHS site information supplied by NHS. These were used in the gap analysis. The use of more comprehensive septic tank information collated by the Improvement Service (IS) was considered. As this data remains incomplete and yet includes a very large number of points its inclusion was felt to not improve the usability of the maps.

Maps of mean ecotoxicological risk for each of the five substances of higher risk, as described in 3.2.4 were produced for surface water sample locations[3]. In these maps the mean ecotoxicological risk is classified in one of five risk groups on a logarithmic scale. The sample locations are shown by scaled symbols which are sized according to the number of samples for each measurement, with larger symbols corresponding to higher sample counts. It was noted that the spatial distribution of the data is highly heterogeneous and that in many locations symbols overlap or obscure adjacent or coincident symbols. Symbols representing higher risk categories were prioritised over lower risk, so where multiple samples are coincident it is those with higher risk which can be viewed on the map. It should be noted that this may present a bias when viewing the map. JPEG format and interactive PDF maps were produced following consultation with the Project Steering Group. Using the free Adobe Acrobat Reader software, the PDF maps may be clicked to reveal information on multiple features allowing the user to view additional tabular or obscured information, and map layers may be switched off or on to simplify the view.

Maps for three substances of higher AMR risk were produced. Individual maps for each of these compounds was produced for surface water, wastewater treatment works (WWTW) influent and WWTW effluent. The symbology for these maps is equivalent to that of the ecotoxicological risk maps.

The maps for ecotoxicological and AMR risk also include Scottish Water WWTW locations. These locations have been grouped into four classes and the symbols scaled according to the Population Equivalent value of each site. The details are shown on each map.

2.8 Limitations

The sections above have outlined limitations with all aspects of the project, including the datasets themselves. In summary, these are:

- Variability in analytical methods
- Variability in statistical methods
- Low confidence in the majority of the PNEC values

3 As environmental risk pertains to risk to aquatic organisms, it would not be relevant to present these risks for non-natural environments such as influents or effluents as they would give the erroneous impression that very high risks exist. For AMR risk this is different, as selection for resistant genes may occur in any environment where bacteria are present, including influents and effluents.

Uncertainties due to a lack of available data are considered in the gap analysis.

In Sweden, the development of the 'List of 25 Environmentally Harmful pharmaceuticals' and the WISE list take information from three distinct sources:

- Janusinfo: a risk- and hazard classification taking into account a risk quotient based on MEC (where available), as well as a score for persistence, bioaccumulation and toxicity; https://janusinfo.se/beslutsstod/lakemedelochmiljo/pharmaceuticalsandenvironment.4.7b57ecc216251fae47487d9a.html).
- The European Medicines Agency (EMA)'s assessment reports (for post-2006 drugs; based on predicted sales data).
- Studies by the Swedish Pharmaceutical Industry published on the Fass website (the industry organization for research pharmaceutical companies operating in Sweden; https://www.fass.se/LIF/startpage), which should be based on actual sales data and updated regularly.

This combined information is evaluated by a panel of experts that includes an environmental toxicologist.

The data readily available at the moment in Scotland are much more limited. The available consumption data requires significant processing before it can be used to calculate PEC and Janusinfo is specific to the Stockholm region. There is no obvious framework for assessment, either in terms of overall prioritisation or for the purpose of comparing alternative prescribing options, nor is a procedure in place to ensure any proposed formulary change is scrutinised by ecotoxicological experts. While this study gives an indication of substances that might be targeted for intervention, it is limited by these issues.

A further limitation exists in the fact that some of the datasets were received late in the project. Due to resource constraints this meant that no PNEC values could be found for substances analysed in these datasets, so that risk for those substances could not be assessed. However, due to the small number of samples in these late datasets it is unlikely that their inclusion in the risk analysis would have resulted in a different prioritisation.

3.0 Findings

This section first describes the datasets included, with a focus on the particular circumstances that may have led to overall higher or overall lower concentrations.

3.1 Description of datasets

Whilst a greater number of studies or datasets than perhaps expected was initially identified through literature review, most of these were outwith the scope in terms of time of sampling (i.e. samples collected prior to 2014). A small number of studies that would have been in scope were not included as data were not received after repeated requests. A full overview of the studies identified through literature review, with indication of inclusion or exclusion (and reasons for exclusion) is available in Appendix X.

Although 20 academics and 11 PhD students were identified through our networking approach, this did not yield any additional studies that were within the scope of the project.

Ten data sources were eventually included (Table 3); it should be noted that there is a slight inconsistency in whether distinct sampling campaigns within the same project are counted separately or not (the noPILLS project is listed as one source, Niemi et al. as three sources). This is of no consequence for the analysis.

The datasets included in the project are described in more detail below.

1 Letsinger et al. 2019 Spatial and temporal occurrence of pharmaceuticals in UK estuaries (20 datapoints)

This paper provides data on the occurrence of pharmaceuticals in estuaries and is the only study included to do so. Ibuprofen, paracetamol, diclofenac, trimethoprim and citalopram were measured in twelve estuaries in the UK. The study focused primarily on the Humber Estuary, where samples were taken every two months over a twelve months' period. In other estuaries, including four in Scotland (Cromarty, Ythan, Forth, and Tay), samples were taken on only one occasion, in August and September 2017 during high tides (±3hrs). A sample was taken in the upper, middle and lower part of each estuary and a single mean value was reported for each estuary.

After the Humber, the Cromarty and Tay estuaries had the highest total concentrations of pharmaceuticals (> 200ngL-^{1}). Of all substances, ibuprofen was found in the highest concentrations in all Scottish estuaries followed by paracetamol in all but the Cromarty Firth, where diclofenac had the second highest concentration.

When considering the risks identified in the current project, it should be noted that it is not entirely clear whether the mean values reported are based on positive detections only. The fraction detected is not reported for the samples taken in estuaries other than the Humber.

Table 3 The datasets included in the project database, with reference numbers used in the project database (NB. There is no number 4 due to a miscommunication in the number allocation process).

Reference No.	Dataset
1	S. Letsinger, P. Kay, S. Rodríguez-Mozaz, Villagrassa, M., Barceló, D., Rotchell, J.M. 2019. Spatial and temporal occurrence of pharmaceuticals in UK estuaries, *Science of the Total Environment*, https://doi.org/10.1016/j.scitotenv.2019.04.182
2	Scottish Water, Chemicals Investigation Programme 2 Scotland (CIP2 Scotland). Unpublished data.
3	Z. Zhang, M. Lebleu, M. Osprey, C. Kerr, and E. Courtot. 2017. Risk estimation and annual fluxes of emerging contaminants from a Scottish priority catchment to the estuary and North Sea. *Environmental Geochemistry and Health 40*: pp. 1-19. https://doi.org/10.1007/s10653-017-0002-y
5	Niemi, L., Taggart, M., Boyd, K., Zhang, Z., Gaffney, P.P.J., Pfleger, S., Gibb, S., 2020. Assessing hospital impact on pharmaceutical levels in a rural 'source-to-sink' water system. Sci. Total Environ. 737, 139618. https://doi.org/10.1016/j.scitotenv.2020.139618
6	SEPA Watch List monitoring. Unpublished data.
7	L. Niemi, S. Gibb, M. Taggart, K. Boyd, Z. Zhang. River Dee pharmaceutical monitoring. Unpublished PhD Research.
8	L. Niemi, S. Gibb, M. Taggart, K. Boyd, Z. Zhang. Pharmaceutical monitoring within the wastewater treatment process. Unpublished PhD Research.
9	S. Ramage, D. Camacho-Muñoz & B. Petrie. 2019. Enantioselective LC-MS/MS for anthropogenic markers of septic tank discharge. *Chemosphere*, 2019 Mar; 219: pp. 191-201 https://doi.org/10.1016/j.chemosphere.2018.12.007
10	noPILLS, GCU. Unpublished data. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=2ahUKEwiP0tf677rpAhW3aRUIHcjBAtQQFjABegQIARAB&url=http%3A%2F%2Fwww.no-pills.eu%2Fconference%2FBS_NoPills_Final%2520Report_summary_EN.pdf&usg=AOvVaw0N9NvKDrTc0-cujn5j-Tg9
11	P. Landova, S. Gibb, M. Taggart. Pharmaceutical monitoring in the River Thurso (Caithness). Unpublished PhD Research.

2 Chemicals Investigation Programme 2 Scotland (CIP2 Scotland) (2105 datapoints)

The data included were provided by Scottish Water and were the result of tranche 1 investigations undertaken as part of the second phase Chemicals Investigation Programme 2 Scotland into a group of substances that are of emerging concern with respect to future regulation under the Water Framework Directive. The study analysed 23 pharmaceuticals sampled monthly over a 2-year period at upstream and downstream of the WWTWs, crude and effluent at 20 low-dilution WWTWs in Scotland providing 1,920 samples. Low-dilution WWTWs were selected based on information gathered from the CIP1 Scotland project to identify WWTWs that could be potentially as risk of failing EQS standards downstream. Further samples were taken in tranche 2 at an additional 24 low dilution WWTWs for the substances identified of concern. This work was carried out with the aim of determining the likelihood that these substances might require the application of controls or remedial measures by the Water Industry if regulation comes into force. Surface water samples were taken upstream and immediately downstream from WWTW and were not taken at WFD compliance monitoring points.

The selection comprised approximately twenty substances including antibiotics, analgesics, anti-hypertensives and antidepressants and some of their metabolites. The concentrations of these substances were determined over the course of 2 years on a monthly basis in wastewater treatment works' influent and effluent, as well as upstream and downstream of the WWTWs, so as to provide an indication of the effectiveness of treatment processes and the possible risks posed by discharges to the environment.

These investigations characterised the concentrations of the chosen substances in untreated sewage and treated sewage effluent, as well as in surface waters upstream and downstream from selected treatment plants. It was shown that the majority of substances studied are removed to a high degree. Those that are less substantially reduced in concentration are ethinyloestradiol, diclofenac, propranolol, the macrolide antibiotics (erythromycin, clarithromycin and azithromycin), fluoxetine, tamoxifen and carbamazepine. Those substances identified for further investigation are azithromycin, clarithromycin, erythromycin, propranonol, diclofenac & EE2 E, E1 & ibuprofen.

When considering the risks identified in the current project, it should be noted that:

- The samples in the CIP2 Scotland programme were taken throughout the two-year period so present no seasonal bias.
- The investigated WWTWs were selected because relatively low environmental dilution was available at those locations, so represent a 'worst case scenario' spatially.

- Surface water samples downstream from the WWTW were taken just outside of the 'mixing zone' and are likely to be elevated compared to 'typical' concentrations in the receiving water body.
- To calculate mean concentrations for each location, 'non-detects' were substituted with ½ LOQ.

3 Zhang et al. Risk estimation and annual fluxes of emerging contaminants from a Scottish priority catchment to the estuary and North Sea (90 datapoints)

This work was the first study to assess the spatiotemporal changes, annual fluxes and ecological risk of emerging contaminants (4 endocrine disrupting chemicals (EDCs) and 6 pharmaceuticals and personal care products (PPCPs) by different monitoring strategies (spot and passive sampling) over 12 months in a Scottish priority catchment (River Ugie, Scotland, 335 km^2). Ibuprofen and carbamazepine were observed to be the dominant contaminants in the River Ugie. The spatiotemporal trend suggested that human activities and medication usages were the primary source of the contaminants. The overall comparison of the two sampling strategies supported the hypothesis that passive sampling tends to integrate the contaminants over a period of exposure and allows quantification of contamination at low concentration. The ecological risk assessment showed that bisphenol A posed the highest risks with 21.5% of the spot samples resulting in a risk quotient greater than 1 (this substance was outside the scope of the current project as it is not a pharmaceutical).

When considering the risks identified in the current project, the following should be noted:

- For comparability, only the spot sampling results have been included in the current project.
- Sampling for this study took place over a 12-month period so present no seasonal bias.
- The mean values reported are based on positive detections only so should be considered alongside the detection frequency.

5 Niemi et al., 2020b. Assessing hospital impact on pharmaceutical levels in a rural 'source-to-sink' water system (40 datapoints)

This study was funded by NHS Highland and Highlands and Islands Enterprise to investigate Caithness General Hospital and the 'source-to-sink' rural water system in Wick. The aim was to determine hospital contribution of pharmaceuticals entering the municipal wastewater system, and pharmaceutical removal in the WWTW. The target compounds were: paracetamol, diclofenac and ibuprofen (analgesics/anti-inflammatories), clarithromycin and trimethoprim (antibiotics), carbamazepine and fluoxetine (psychiatric drugs) and 17α-ethinylestradiol (synthetic hormone). Samples were collected daily for one-month (Feb 2018) from: (i) raw water supply; (ii) treated hospital tap water; (iii) hospital wastewater discharge; (iv) combined WWTW influent; and (v) final WWTW effluent. Concentrations ranged from: 3 ng/L (carbamazepine) to 105910 ng/L (paracetamol) in hospital discharge; 5 ng/L (ibuprofen) to 105780 ng/L (paracetamol) in WWTW influent; and 60 ng/L (clarithromycin) to 36201 ng/L (paracetamol) in WWTW effluent. WWTW removal ranged from 87% (paracetamol) to <0% (carbamazepine and clarithromycin), and significant correlations with water quality characteristics and WWTW flow data were observed for some compounds.

When considering the risks identified in the current project, the following should be noted:

- Non-standard environmental matrices were included in this study (treated drinking water, hospital discharge, WWTW primary sample, WWTW secondary sample).
- Mean values were reported based on positive detects, concentrations <LOQ were considered non-detects and not included in calculations.

6 SEPA Watch List Monitoring Dataset (154 datapoints)

Under the Water Framework Directive (WFD), the surface water Watch List (WL) is a list of potential water pollutants that should be carefully monitored by the EU Member States to determine the risk they pose to the aquatic environment and whether EU Environmental Quality Standards (EQS) should be set for them. In Scotland, SEPA is responsible for doing so and the concentrations included in this project are based on the results of this undertaking.

Although only a small number of pharmaceuticals are on the WL, data on a much larger number of compounds was received. Due to resource limitations, it was not possible to include all of these. Instead, compounds were screened against priority lists and against those already included in other studies, so that they could add to the completeness of our understanding of those compounds. Chemical analysis was carried out by subcontracted laboratories and information on the detail of the chemical method was limited.

Two points should be noted in terms of data processing:

- In the SEPA dataset, a small number of samples was recorded without a value or LOQ, e.g. "Cas# 113665-84-2 Clopidogrel". As in these cases it was not possible to substitute ½ LOQ, these values were omitted (i.e. those samples are not included in the number of samples 'n').

- Values reported as <LOQ have been included in calculations as ½LOQ.

7 Niemi et al. River Dee Pharmaceutical Monitoring (64 datapoints)

This study monitored pharmaceuticals and water quality in the River Dee, Aberdeen over a 12-month period (Aug 2018 – 2019). Compounds were the same as in study number 5. Grab and passive sampling were performed twice a month, every two months at eight sites spanning from upstream of Braemar to the estuary line in Aberdeen city. Sites of interest included downstream of the wastewater treatment plants in Banchory and Aboyne, and upstream of the drinking water abstraction sites in Banchory and Cults. Compounds including ibuprofen (anti-inflammatory), paracetamol (analgesic), trimethoprim (antibiotic) and carbamazepine (anti-epileptic) were detected in the mid nanogram per litre concentration range, with sharp spikes in concentrations observed directly downstream of wastewater treatment plants.

When considering the risks identified in the current project, the following should be noted:

- For comparability, only the grab sample results were included in the CREW project,
- Sampling in the River Dee was performed during the summer 2018, but flow conditions and seasonal variations were not reported. This may need further consideration due to drought in summer 2018
- Mean values were reported based on positive detects, concentrations <LOQ were considered non-detects and not included in calculations.

8 Niemi et al. Pharmaceutical monitoring within the wastewater treatment process (40 datapoints)

In this study, which targeted the same compounds as studies 5 and 7, samples were collected over seven weeks (May-July 2018) from Caithness General Hospital (Wick) and four sites within the Wick WWTW: raw influent, primary sample, secondary sample and final effluent. Paracetamol and ibuprofen were detected in highest concentrations in all samples, while 17a-ethinylestradiol was never detected. The antibiotics trimethoprim and clarithromycin were recalcitrant to removal, with final effluent concentrations exceeding influent concentrations.

When considering the risks identified in the current project, the following should be noted:

- Non-standard environmental matrices were included this study (WWTW primary sample and WWTW secondary sample),
- Mean values were reported based on positive detects, concentrations <LOQ were considered non-detects and not included in calculations.

9 Ramage et al. Enantioselective LC-MS/MS for anthropogenic markers of septic tank discharge (28 datapoints)

This study investigated septic tanks as a potential source of pharmaceutical pollutions, targeting 16 compounds in samples collected in North East Scotland. The study found caffeine to be ubiquitous in all samples studied suggesting it as a good indicator of septic tank discharge. In rural streams studied, concentrations of all prescription drugs investigated were ≤0.02 µg L^{-1}. However, analgesics and stimulants were at high concentration in one location indicating direct discharge of septic tank wastewater (i.e., not dissipated through a soak away). For example, paracetamol, cotinine and caffeine were measured at 1100 µg L^{-1}, 31 µg L^{-1} and 200 µg L^{-1}, respectively, which is comparable to septic tank effluents.

This dataset contained enantioselective analysis, which quantified enantiomers of chiral pharmaceutical compounds. This included analysis of both the R(-) and S(+) enantiomers of amphetamine, atenolol, chlorpheniramine, citalopram, fluoxetine, propranolol and salbutamol in septic tank effluent and effluent-receiving river water (Ramage et al., 2019). The purpose of the selectivity and specificity of this study was to investigate the occurrence of potentially enantiospecific toxic pharmaceuticals in wastewater and surface water (Ramage et al., 2019). Evidence suggests that one enantiomer may contain great pharmacological activity than the other; this may lead to differences in NHS prescribing practices between specific enantiomers and racemic mixtures (i.e., a drug containing both R(-) and S(+) enantiomers). Amphetamine (a stimulant) is prescribed in racemic mixture as the drug Lisdexamphetamine, while the drug Dexamphetamine contains only S(+)-amphetamine (NHS, 2018a). Similarly, citalopram (an antidepressant) is prescribed as both Escitalopram (S(+)-citalopram) and Citalopram (racemic mixture) (NHS, 2018b, NHS, 2018c). Of the other target compounds in the Ramage et al., (2019) study, analysis suggested greater pharmacological activity of one enantiomer. This is the case for S(+)-atenolol (Stoschitzky et al., 1993), S(+)-chlorpheniramine (Koch et a., 2020), R(-)-fluoxetine (Koch et al., 2002, Magyar et al., 2003), S(+)-propranolol (Stoschitzky et al., 1995), R(-)-salbutamol (Westerhof et al., 2005). In order to compare this study with the non-enantioselective data, concentrations were reported as the sum of the two enantiomers. The highest limit of detection/ quantitation and lowest recoveries were reported in these cases, as advised by the data holder. Furthermore, S(+)-amphetamine and R(–)-amphetamine were present in this stream sample at 0.20 and 0.27 µg L^{-1}. This corresponds

to an enantiomeric fraction of 0.43, which is typical of untreated wastewaters in the UK. The authors conclude that further study on the diffuse impact of septic tanks to surface water is needed and can be supported using this new multi-residue enantioselective method.

It may have been most appropriate to retain the enantiomer specific concentrations of R(-) and S(+) citalopram and amphetamine, as these drugs are prescribed differently; however, comparability between datasets and preserving clarity in the GIS mapping exercise were the ultimate goal of the current phase of this project. Future work may seek to explore enantiomer specific concentrations of pharmaceuticals in the environment.

When considering the risks identified in the current project, it should be noted that:

- Samples for this study were single grab samples
- Samples were collected in June 2018. Although the authors do not report flow conditions, these may have been low as 2018 was an unusually dry summer.

10 GCU noPILLS (https://keep.eu/projects/7008/) (500 datapoints)

In Scotland, sampling took place at the influents and effluents of two WWTW, one using mainly trickling filter technology (TF) and one using mainly conventional activated sludge technology (CAS), and upstream and downstream in the receiving waters. For each WWTW, two 4-day sampling campaigns were undertaken, one in a dry week and one in a wet (rainy) week.

Notable findings included that carbamazepine, lidocaine, erythromycin and clarithromycin were hardly removed. Diclofenac was removed somewhat better. The common analgesics paracetamol, ibuprofen and naproxen were all well removed. Values were generally in good agreement with the literature; however, atenolol and diclofenac were removed better than suggested by the literature whilst clarithromycin and amoxicillin were not removed as well as in previous studies.

In addition, samples were taken from 7 locations in the River Almond catchment on 4 consecutive days to gain an understanding of spatial variation in the catchment. The River Almond (West Lothian) catchment is highly urbanised; the river and its tributaries receive effluent from multiple WWTW as well as numerous smaller discharges such as from septic tanks. To investigate spatial variation, daily grab samples were taken at seven locations in the upper and middle sections of the catchment. Eleven investigated compounds were detected at all locations but one, at concentrations mostly in the high ngL^{-1} range but up to 14 μgL^{-1} (erythromycin), indicating these compounds are ubiquitous in the catchment. Four of these, ciprofloxacin, ibuprofen, and the two macrolide antibiotics erythromycin and clarithromycin that feature on the Watch List were consistently found at toxicologically relevant concentrations in several locations. Some compounds were detected in a small tributary upstream from any WWTW input, and, comparing two locations 10km apart with no WWTW effluent inputs in between, several compounds were detected at similar or even higher concentrations at the location 10 km downstream. Although further research is necessary, these results suggest that non-WWTW discharges (e.g. septic tanks, veterinary sources) may contribute to overall levels of pharmaceuticals in this small stream.

When considering the risks identified in this project, it should be noted that:

- Surface water sampling was carried out in summer during periods of relatively low flow.
- Mean values were calculated as the mean of the positive detections only so should be considered alongside the detection frequency.

11 Landova et al. Pharmaceutical monitoring in the River Thurso (Caithness) (32 datapoints)

This work performed an initial investigation into pharmaceutical presence in the River Thurso (Caithness), with sampling through grab and the newly developed passive technique. The target pharmaceuticals were the same as those listed in the above Niemi studies. Five sampling events were performed at four sites over a three-month period in summer 2018. Paracetamol, ibuprofen, carbamazepine and clarithromycin were detected in the greatest number of samples, and at the highest concentrations in surface water. 17α-ethinylestradiol, fluoxetine and diclofenac were not detected in the River Thurso.

When considering the risks identified in the current project, the following should be noted:

- For comparability, only the grab sample results were included in the CREW project,
- Sampling in the River Thurso was performed summer 2018, but flow conditions and seasonal variations were not reported. This may need further consideration due to drought in summer 2018
- Mean values were reported based on positive detects; concentrations <LOQ were considered non-detects and not included in calculations.

3.2 Quantitative findings

This section describes some of the most notable findings. Due to resource constraints we focused primarily on identifying those compounds posing the greatest risk to

the environment and risk in terms of AMR.

Comparing risk thresholds for aquatic organisms and for driving selection for resistance, we can see that for most antibiotic compounds, PNEC(ENV) is lower than PNEC(AMR), in other words, the protection of aquatic organisms would require stricter concentration limits than the prevention of AMR proliferation. For ciprofloxacin, the two values are similar, and for oxytetracycline, PNEC(AMR) is the lower value (Table 4).

Table 4 Comparison of PNEC(ENV) and PNEC(AMR) for the antibiotic compounds.

Compound	PNEC(ENV) (µg/L)	PNEC(AMR) (µg/L)
Azithromycin	0.019	0.25
Ciprofloxacin	0.089	0.064
Clarithromycin	0.12	0.25
Erythromycin	0.2	1
Trimethoprim	0.0058	0.5
Sulfamethoxazole	0.59	16
Oxytetracycline	18	0.5

3.2.1 Concentrations

In untreated hospital effluent, the highest concentrations reported were for paracetamol, with a mean value of 33 μgL^{-1}, with a detection frequency of 100%. The maximum concentration was 105.91 μgL^{-1}. Ibuprofen and clarithromycin were also encountered at mean values great than 1 μgL^{-1}. Only one study of hospital wastewater was included and this cannot be taken to represent other, larger hospitals. The PILLS project, which preceded the noPILLS project and was outwith the date range considered, investigated hospital wastewater at two community and two general hospitals, in rural and urban settings. The project report is available on request but it should be noted that significant changes to the hospital infrastructure have since taken place.

The noPILLS project found paracetamol at very high concentrations in two WWTW influents. More broadly, based on the larger CIP2 Scotland study, metformin is usually found at the highest concentrations, reaching between 70 and 200 μgL^{-1} in 16 locations. While some other compounds are occasionally high, ibuprofen is the next highest overall in influent with concentrations frequently in tens of micrograms.

In effluent, again the noPILLS project reported high values for paracetamol, but metformin is present at the highest concentrations in the effluents in the CIP2 Scotland programme. However, no clear second place compound emerges, indicating that removal efficiencies play an important role in determining what is released to the environment.

In surface waters, both Ramage et al. (2019) and the noPILLS project report extremely high concentrations for paracetamol in one location each, into hundreds of micrograms although with a detection frequency of around 40% in both cases. Mean values of caffeine, carbamazepine, erythromycin and metformin all reach > 10 μgL^{-1} in certain locations. Quite a number of different compounds reach mean concentrations greater than 1 μgL^{-1} in at least one location, including caffeine, metformin, carbamazepine, erythromycin, cotinine, ranitidine, propranolol, the metabolite norerythromycin, and atenolol.

3.2.2 Ecotoxicological risk

To determine risk, environmental concentrations are compared with PNEC(ENV) as an ecotoxicological threshold. Below, mean RQ(ENV) refers to the RQ(ENV) value calculated from the mean concentration value for the compound at a specific location. It should be noted that ecotoxicological risk could therefore only be determined where a PNEC value is available; gaps in the PNEC dataset are discussed in section 3.3.1. In addition, it should be noted that even where PNEC values are available, not all compounds are subjected to the same array of tests (see also section 4 Discussion). Importantly, limitations discussed in section 2.6.2 and Appendix IX with regard to PNEC reliability apply.

For this section, only surface water concentrations were considered, as inclusion of concentrations in effluents and other environmental matrices would give an inflated impression of risk. Mean RQ values were used, because the PNEC values refer to chronic exposure conditions. It could be appropriate to compare the RQ(ENV) based on maximum concentrations with acute toxicity thresholds, as these represent higher but sporadically encountered concentrations, but this was beyond the scope of this project.

Database analysis of ecotoxicity risks

Bearing these limitations in mind, ibuprofen dominates in terms of environmental risk (although again it should be noted that the test on which its low PNEC value is based has not been carried out for all compounds). Again, the highest mean RQ(ENV) are based on the noPILLS data, with $RQ(ENV)_{ibuprofen}$ between 35 and 95 in 10 locations in this study alone. Other studies, including those with year-round sampling campaigns, find similarly and in total, mean RQ(ENV) for this compound exceeds 10 in 34 locations, indicating a very high environmental risk.

Other compounds with mean RQ(ENV) > 10 include erythromycin (four times), trimethoprim (twice), triclosan, propranolol, venlafaxine, diclofenac, E2, ranitidine, and norethromycin (all once).

A wide range of compounds was found with mean RQ(ENV) > 1 in at least one location, giving a total of 217 data points indicating environmental risk.

Visual analysis of the maps (Appendix V) displaying the ecotoxicological risks posed by the substances of higher risk

Due to the symbol size on the map, which had to be large enough to be visible on the national scale, the difference between 'upstream and downstream' measurements in the CIP2 Scotland dataset is not easily visible and the downstream symbol (typically the higher risk result) mostly obscures the upstream result (as higher risk results are displayed on top of lower risk results). The CIP2 Scotland dataset was the largest dataset included. Given that the downstream samples were taken immediately downstream from the mixing zone for WWTWs with the lowest dilution available, visual analysis of the risk maps may thus lead to an overestimation of overall risk levels. While these caveats, as well as issues of comparability of the datasets previously discussed, some overall impressions can be gleaned from visual analysis of the risk maps.

It appears that ibuprofen is found to pose a risk almost wherever it is found. With a high detection frequency, it is clearly ubiquitously present in concentrations higher than the risk threshold.

Despite high values at a few locations as noted above, erythromycin appears to be mostly present in concentrations below PNEC, with the exception of the results from the noPILLS study. It is possible that RQ > 1 occurs more widely in dry conditions and the ecological impact on periodic exceedances is not well understood.

EE2 is found to pose a risk predominantly in the Central Belt area, with RQ values mostly between 0.1 and 10. Although it was targeted for analysis in the River Dee, it did not appear to pose a risk there.

Ecotoxicological risks for clarithromycin tend to be slightly higher, but mostly still in the same order of magnitude to those of erythromycin. Risk is low in the River Dee.

Notably, diclofenac poses a very high risk (RQ > 10) at the Clyde Tidal Weir. It does not appear to pose a risk in the North-East of Scotland. Otherwise, most values are between 0.1 and 10.

3.2.3 AMR-related risk

In terms of AMR-related risk, the project team found that a much larger number of pharmaceutical compounds than perhaps expected have antibacterial properties. Not only the antibiotics investigated and the antimicrobial compound triclosan, but also ibuprofen, paracetamol, diclofenac, fluoxetine, propranolol, and 17-beta oestradiol. A full list with details of the extent of agreement within the literature, is given in Appendix VIII.

For antibiotics, we were able to quantify risks by comparing concentrations with PNEC(AMR) values taken from Bengtsson-Palme and Larsson (2016).

Database analysis of AMR Risk

In surface waters, three compounds had RQ(AMR) >1: erythromycin, clarithromycin and ciprofloxacin. The highest risks encountered overall were for erythromycin concentrations found in the noPILLs study, which represented relatively low flows (NB the calculation of the mean was of little influence as the detection frequencies were typically very high). The maximum RQ(AMR) for this compound was just over 11 and RQ(AMR) was greater than 1 in six locations. In the other datasets however, RQ(AMR) for erythromycin did not exceed 0.34, indicating low risk. We did not investigate whether erythromycin prescribing follows seasonal patterns, but the findings here appear to suggest that the variation in flow, with lower flows in summer, outweighs any increase in prescribing over the winter period.

In the CIP2 Scotland programme, which reflects a longer sampling period throughout the two years, clarithromycin presents the highest-ranking AMR risk, although RQ > 1 in only two locations. RQ(AMR) for ciprofloxacin also exceeded 1 in two locations, both in the noPILLS study.

In other environmental media, the same three compounds accounted for the overwhelming majority of occasions where RQ(AMR) >1, although trimethoprim and azithromycin also featured. It should however be noted that trimethoprim was not investigated in either the noPILLS study or the CIP2 Scotland programme, and may be more widespread than we are able to ascertain. Erythromycin has an RQ(AMR) > 10 in one effluent, measured in the noPILLS project, and in six WWTW influents, measured in the CIP2 Scotland programme. More than 100 measurements of antibiotics in influents and effluents resulted in RQ(AMR) > 1. Mechanisms that cause antibiotics to drive selection for resistance apply in any environmental matrix, so this is a potential concern.

Visual analysis of the map displaying AMR risks posed by the selected antibiotics (Appendix VI)

The main risk in terms of driving selection for resistance appears to be from ciprofloxacin and clarithromycin in WWTW influent, where RQ(AMR) is greater than 10 in a number of locations. In effluent, RQ for clarithromycin is still > 1 in many locations, although for ciprofloxacin the risk is considerably less in effluent and surface water, suggesting that it is removed reasonably well from the aquatic phase. Risks for erythromycin are mostly below 1,

but this compound appears to be poorly removed – risks in surface waters are still mostly between 0.1 and 1.

3.2.4 Overall prioritisation

The Water Framework Directive (WFD) sets out a "Strategy against pollution of water" requiring the European Commission to propose Priority Substances (PS) that present a significant risk to or via the aquatic environment (Directive 2000/60/EC). When choosing the priority substances the following should be taken into account: 1) evidence regarding the intrinsic hazard of the substance concerned, and in particular its aquatic ecotoxicity and human toxicity via aquatic exposure routes; 2) evidence from monitoring of widespread environmental contamination; and 3) other proven factors which may indicate the possibility of widespread environmental contamination, such as production or consumption by mass of the substance concerned, and use patterns.

From the total list of compounds monitored in the various studies, the aim was to choose 5 substances for which to visualise risk through the mapping exercise. To this end, we identified the 20 compounds with highest risk by ecotoxicity (RQ(ENV); the 20 compounds with the highest detection frequency (DF); and the 20 with highest consumption (by weight) (Table 4). In addition, regulatory interest was taken into account.

The basis for the consumption data analysis was a study by Helwig et al. (2016), which used NHS data from 2014 on prescription in the community (Prescribing Cost Analysis dataset) and in hospitals (Hospitals Medicines Utilisation Database). This study was not complete for all compounds in our study, but due to time constraints it was not possible to conduct a new analysis. DF (%) is calculated as the number of positive detections divided by the total number of samples in the collated data. The potential ecological risks of the contaminants were assessed based on risk quotient (RQ) approach following the Technical Guidance Document on Risk Assessment from the European Commission (2018). As discussed previously, the RQ values of contaminants are calculated by dividing the measured environmental (mean surface water) concentration (MEC) by the predicted no-effect concentration (PNEC[4]) for each chemical (Equation 2). For the purpose of interpreting the risk calculations, the RQ values were classified into the following four levels: minimal risk (RQ<0.01), low risk (0.01≤RQ<0.1), medium risk (0.1≤RQ<1) and high risk (1≤ RQ). The values of risk in Table 4 represent the monitoring points at each different level by mean concentration.

Based on the holistic consideration of risk, detection frequency and usage data from the top 20 chemicals (Table 4), particularly the level of the potential ecological risks and also taking account of the coverage of different therapeutic groups, 5 compounds were chosen to be taken forward into the mapping exercise:

- ibuprofen
- clarithromycin
- erythromycin
- diclofenac
- EE2.

For a slightly more extensive list and future visualisations, three further compounds are suggested for inclusion:

- metformin
- ranitidine
- propranolol.

With these additions, the selected substances represent a wide range of main therapeutic groups including antibiotics, analgesics, hormones, biguanides, proton pump inhibitors and anti-hypertensives. However, this is not to suggest that no other compounds pose a risk, as is evident from Table 4, and priorities should be re-evaluated depending on the context of any future project or initiative. Triclosan is used as an antibacterial drug in (for example) skin creams, but also – more commonly - as a biocide in non-pharmaceutical applications. For this reason, it was not selected for the purposes of this project.

3.3 Gap analysis

This section reports solely on the analysis of whether sampling has been performed within the Scottish environment (over the five-year period), and not on results (e.g., mean concentrations, detection frequency, number of samples). The five substances identified as posing a higher risk (ibuprofen, clarithromycin, erythromycin, diclofenac and 17α-ethinylestradiol) were included separately in the gap analysis.

3.3.1 Compounds for which environmental data is lacking

The 60 pharmaceutical compounds included in this study were compared to priority lists including the Stockholm list of 25 drugs identified as 'Environmentally Harmful' (2020), the European Union Water Framework Directive 2018 Watch List (6 compounds; Loos et al., 2018) and the UKWIR Chemical Investigation Programme (23 compounds; Boxall et al., 2014). Also included was a recent study of the top prescribed pharmaceuticals by environmental risk in Scotland (19 compounds; Helwig et al., 2016). Based on these lists, monitoring data in

4 For detail on the sources of PNEC values, please see Appendix IX.

Table 5 Twenty compounds with consumption, detection frequency (DF %) and ecological risk								
Compound	**Consumption (kg) (based on Helwig et al. 2016; data from 2010/11)**	**Total number of samples**	**Positive detections**	**DF%**	**Minimal Risk**	**Low Risk**	**Medium Risk**	**High Risk**
Azithromycin		988	980	99	5	9	25	7
Carbamazepine	4909	1294	1152	89	42	41	5	1
Ciprofloxacin	1319	1054	956	91	14	41	7	2
Clarithromycin	98	1215	1103	91	21	12	46	8
Diclofenac	3177	1350	1190	88	23	24	41	16
E1 - estrone		1258	1218	97	0	14	48	6
E2 - 17β-estradiol		1217	1120	92	0	1	48	19
EE2 - 17α-ethinylestradiol	1	1221	1111	91	12	0	38	20
Erythromycin	2086	1167	1120	96	1	31	34	16
Fluoxetine	683	1060	965	91	19	15	20	2
Ibuprofen	16289	1280	1190	93	3	0	9	76
Metformin	67132	980	980	100	1	18	27	0
Naproxen	4671	9	9	100	0	3	1	0
Paracetamol	328484	324	191	59	41	5	3	3
Propranonol	1020	1091	1038	95	13	10	38	5
Ranitidine	4645	1060	1010	95	12	9	35	5
Sertraline	791	971	971	100	10	25	8	0
Sulfamethoxazole		108	25	23	14	7	2	0
Triclosan		1117	1091	98	0	4	31	20
Trimethoprim	1064	103	37	36	9	1	3	7

Scotland is missing for 18 compounds (Table 5). All compounds included in the Water Framework Directive Watch List have been monitored in Scotland. Escitalopram, listed in the Stockholm List of Environmentally Harmful Pharmaceuticals, was monitored in one study by Ramage et al. (2019), but was reported with citalopram (refer to section 2.3.3 on data processing).

3.3.2 Compounds for which threshold data is lacking

The literature search for PNEC(ecotox) data was conducted in October 2019 and of the compounds included in the project database at that time, gabapentin was the only one for which no PNEC value could be found.

Table 6 Compounds for which environmental data is lacking in Scotland			
Therapeutic Group	**Compound**	**Therapeutic Group**	**Compound**
Antibiotic	Amoxicillin [1,3,4]	Antihistamine	Meclizine [1]
	Flucloxacillin [4]		
	Penicillin V [4]	Antipsychotic	Flupenthixol [1]
	Piperacillin [4]		Haloperidol [1]
	Roxithromycin [1]		Risperidone [1]
	Tetracycline [1]		
Antibacterial	Tazobactam [4]	Antiseptic	Povidone-iodine [4]
Antidepressant	Escitalopram* [1]	Calcium channel blocker	Felodipine [1]
Antidiabetic	Glibenclamide [1]	Contraceptive	Levonorgestrel [1]
Antifungal	Clotrimazole [4]	Uric acid reductant	Allopurinol [4]

*monitored in 1 study but reported as citalopram in the CREW database. [1] Stockholm list of 25 drugs identified as 'Environmentally Harmful' (Appendix II); [2] European Union Water Framework Directive 2018 Watchlist (Loos et al., 2018); [3] UK Water Industry Research Chemical Investigation Programme (Boxall et al., 2014); [4] top listed prescribed pharmaceuticals by environmental risk in Scotland (Helwig et al., 2016).

Late on in the project, some further datasets were added; due to resource constraints it was not possible to carry out additional literature search for the 'new' compounds (10,11 di-hydroxy carbazepine; amphetamine; chlorpheniramine; cotinine; gliclazide; methylparaben; N-acetylsulphamethoxazole; and salbutamol.

For a number of compounds, only a modelled PNEC value could be found, based on either ECOSAR or QSAR structural analysis models. These are benzoylecgonine, citalopram, clotrimazole, cocaine, meclozine, lorazepam, and venlafaxine.

As mentioned before, the AF used in PNEC calculation is an indication of the amount and type of ecotoxicity data available (see 2.4.1). PNEC values with an AF of 1000, indicating that only acute toxicity studies were available, were found for bezafibrate, caffeine, diazepam, glibenclamide, ifosfamide, iohexol, lidocaine, mefenamic acid, omeprazole, and risperidone. PNEC values with AF 100, indicating only one long-term ecotoxicity study was available, had to be used for amitriptyline, amoxicillin, and iopromide. PNEC values with AF50, indicating two long-term results from different trophic levels, were used for cyclophosphamide, fluvoxamine, orlistat, paroxetine, and trimethoprim.

We have not assessed the robustness of the PNEC values supplied by the OHBP partners.

3.3.3 Spatial gaps in environmental data

Gaps by environmental matrix

Ten distinct environmental matrices monitored across Scotland were included in the database, including surface water (river or stream, loch, estuary), WWTW media (influent, effluent, primary and secondary), septic tank effluent, hospital sewage (untreated) and mains drinking water. Of all the samples, surface waters (rivers or streams) represented the majority of sampling locations in the database with 1781 datapoints (58% of total database) (Figure 1). WWTW effluent (629 datapoints, 20%) and influent (577 datapoints, 19%) followed. Limited monitoring data was observed for estuary (20 datapoints, 1%), loch (16 datapoints, 1%), or septic tank effluent (10 datapoints, 0%). 'Other' accounts for 1% of the database, and comprises untreated hospital sewage (16 datapoints), WWTW primary (8 datapoints), WWTW secondary (8 datapoints) and mains drinking water (8 datapoints). Several water body types were monitored in single studies which focussed on specific regions. The mains drinking water, WWTW primary, WWTW secondary and untreated hospital sewage were monitored in Caithness (Highlands), and the septic tank effluent was monitored in Aberdeenshire.

The five substances of higher risk followed similar trends to the total dataset. Most monitoring was performed in surface waters for ibuprofen, clarithromycin, erythromycin, diclofenac and 17α-ethinylestradiol (Figure 2). None were monitored in septic tank effluent, and only ibuprofen and diclofenac were monitored in estuarine surface water. Limited monitoring for these compounds has been performed in loch surface water.

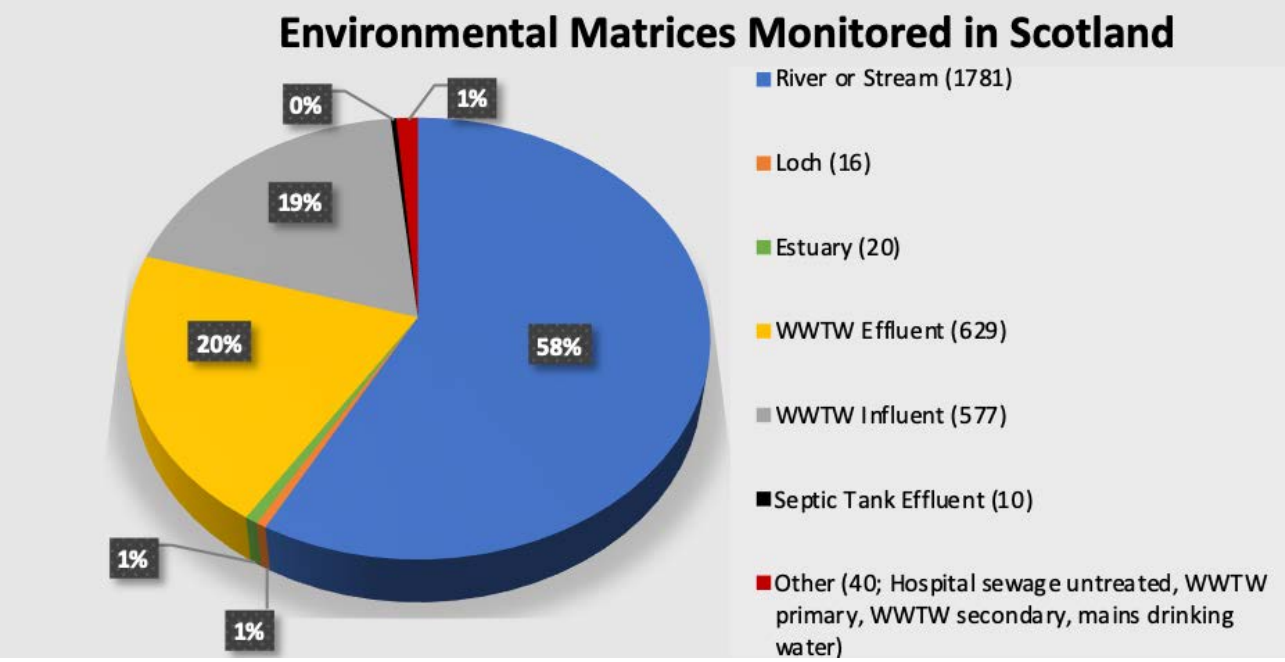

Figure 2 Environmental matrices monitored in Scotland, with number of datapoints.

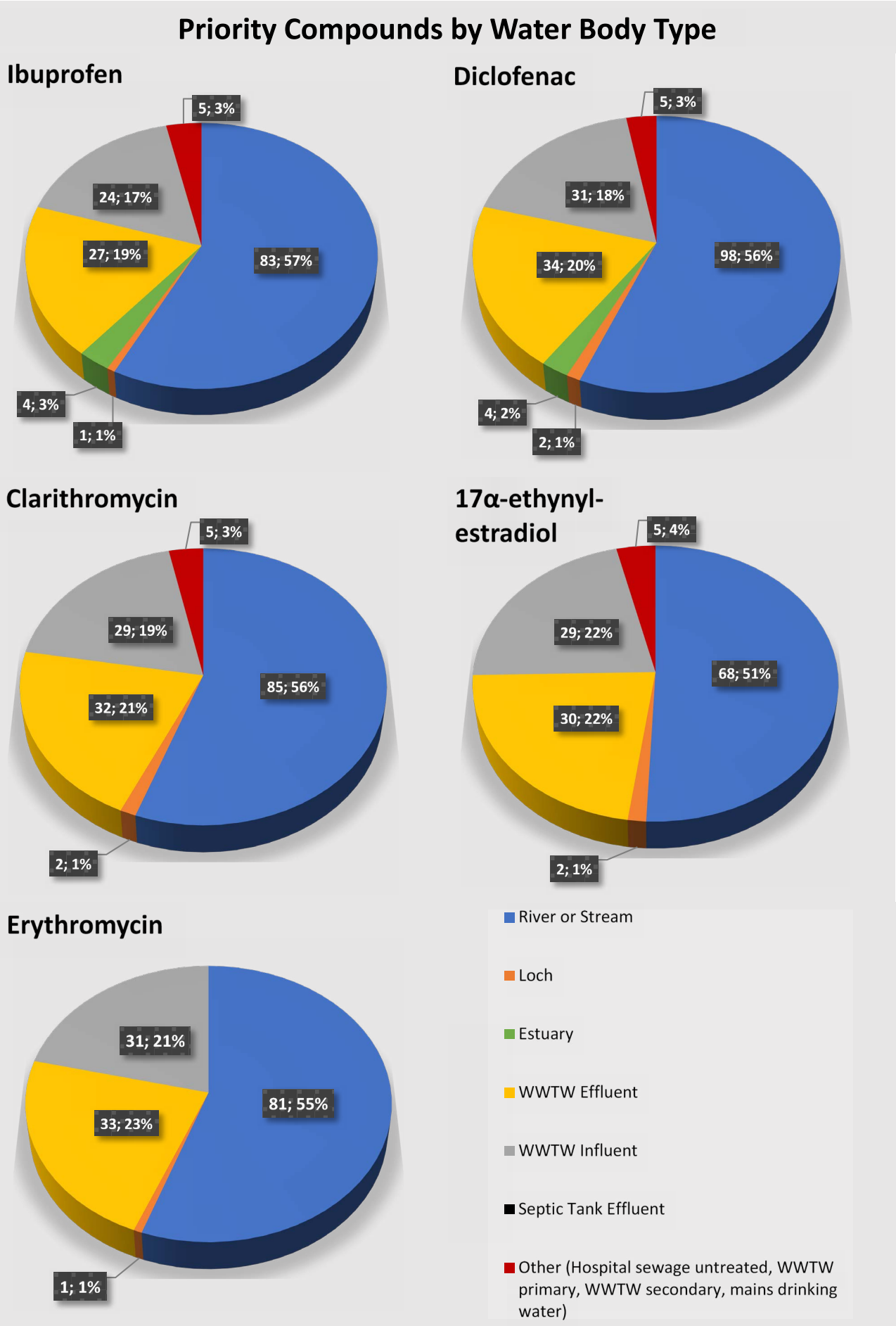

Figure 3 Priority compounds by environmental matrix monitored in Scotland, with number of datapoints indicated by percentage value.

Gaps by WFD water body type

As part of WFD classifications, different types of water body are distinguished: river, loch, estuary, coastal and groundwater. We already mentioned that no results were available for coastal and ground water and that estuarine findings were taken from one study only (Letsinger et al. 2019).

Gap analysis by surface water type only was performed for comparison of the database monitoring data with the SEPA record of Scottish 3,652 water bodies (SEPA, 2018). The selected surface water media from the database were river or stream, estuary and loch, for which there were 19, 4 and 2 distinct water bodies monitored in the CREW database, respectively (Figure 3). No monitoring data was available for ground water, coastal or marine waters, and it is evident very limited data was present for surface water estuaries and lochs. Comparison reveals that little overall monitoring in surface water across Scotland has been performed, with a small fraction (<1 %) of Scottish water bodies having existing pharmaceutical monitoring data.

Gaps by Local Authority Area

There are 32 local authorities in Scotland (mainland and islands). A total of 14 local authority areas had pharmaceutical monitoring data, including: Aberdeen City, Aberdeenshire, Angus, City of Edinburgh, East Lothian, Fife, Glasgow City, Highland, Midlothian, North Lanarkshire, South Lanarkshire, Perth and Kinross, Stirling and West Lothian. Most data were available for West Lothian (944 datapoints, 31% of data in the database), North Lanarkshire (324, 11%) and Aberdeenshire (293, 10%), as shown in Figure 4. Little monitoring data was available for Aberdeen City (61 datapoints) and Angus (48 datapoints), each corresponding to only 2% of the database. Ibuprofen, clarithromycin, erythromycin, diclofenac followed the same trend as the total database, with most data from monitoring in West Lothian and Aberdeenshire and the least available in Aberdeen City and Angus (see Appendix XI, Figure XI-1).

No pharmaceutical monitoring has been performed in the remaining 15 mainland local authorities: Argyll and Bute, Ayrshire (North, South and East), Clackmannanshire, Dumfries and Galloway, Dunbartonshire (East and West), Dundee City, Falkirk, Inverclyde, Moray, Renfrewshire, East Renfrewshire, and the Scottish Borders. Additionally, no monitoring has been performed in the three island authorities: Na h-Eileanan an Iar (Outer Hebrides), Orkney Islands and Shetland Islands. It is evident that most monitoring has focussed in the "Central Belt" region of Scotland, including Glasgow, Lanarkshire, Edinburgh, Lothian and Fife. Local authorities within this region have the highest population and population densities across Scotland (Figure 5). However, urban regions such as Aberdeen City, Dundee City, Dunbartonshire (East and West) and Renfrewshire, which have both high population and population density, have little or no monitoring data. Additionally, the rural regions on the mainland lack representative monitoring data (e.g., Argyll and Bute, Dumfries and Galloway, the Scottish Borders, Moray, Highlands). Rural areas such as these may have low population density across the entire local authority, but densely populated towns or cities may be present within the region.

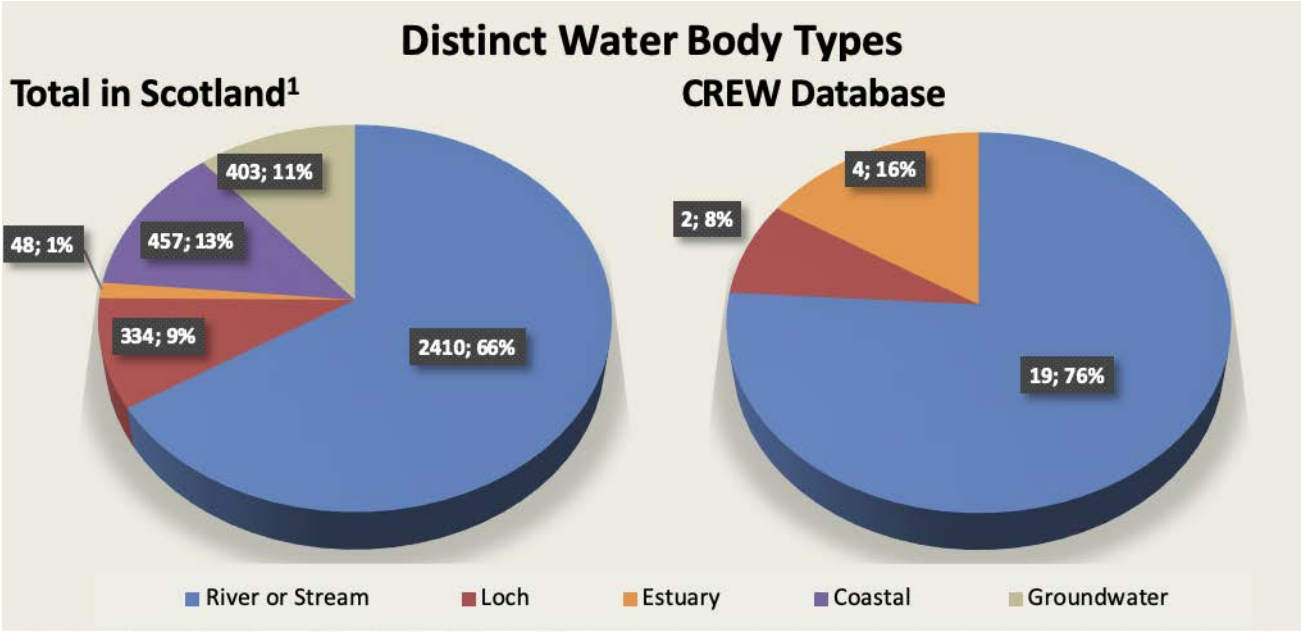

Figure 4 WFD water bodies in Scotland (3,652) (SEPA, 2018) compared to distinct locations monitored in the project database (25), with number of datapoints and percentage value.

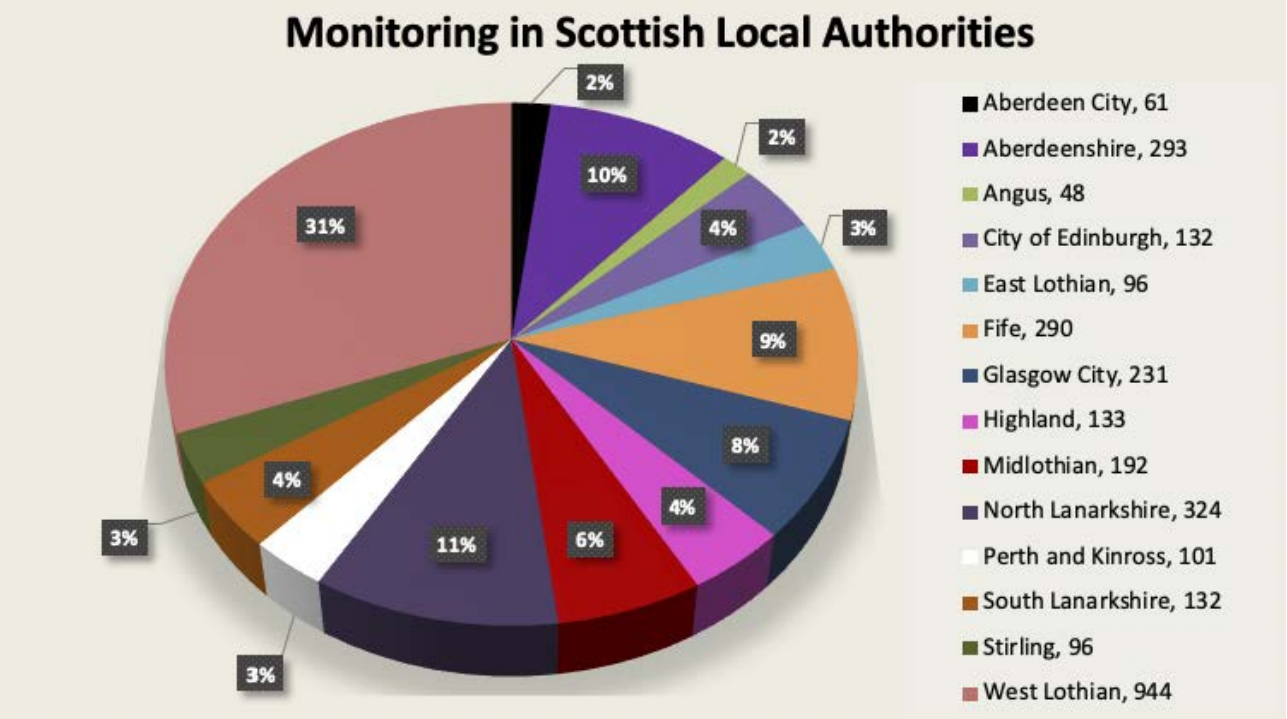

Figure 5 Scottish Local Authorities (14 in total) with monitoring data, with number of datapoints and percentage.

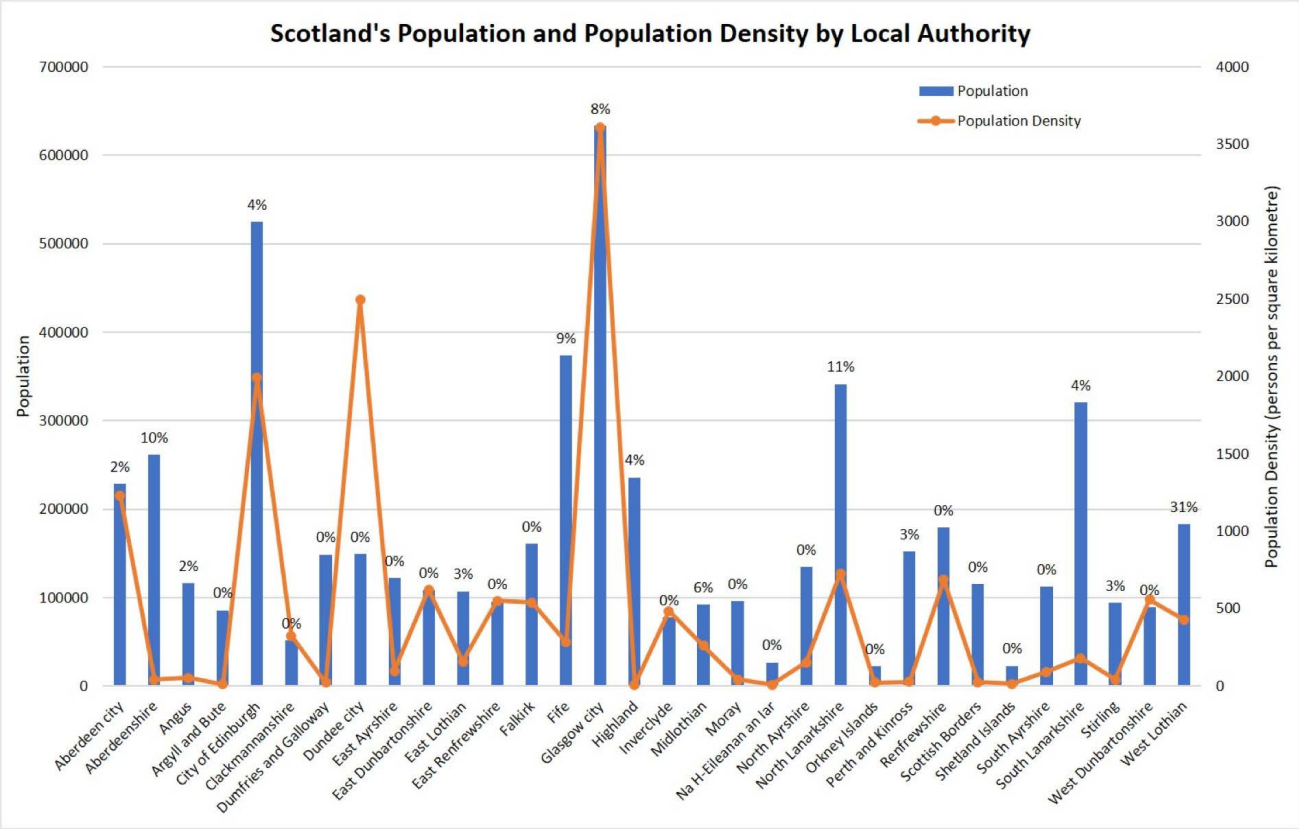

Figure 6 Population and population density in the 32 Scottish local authorities, data labels show percentage of pharmaceutical datapoints in the database (National Records of Scotland, 2019)

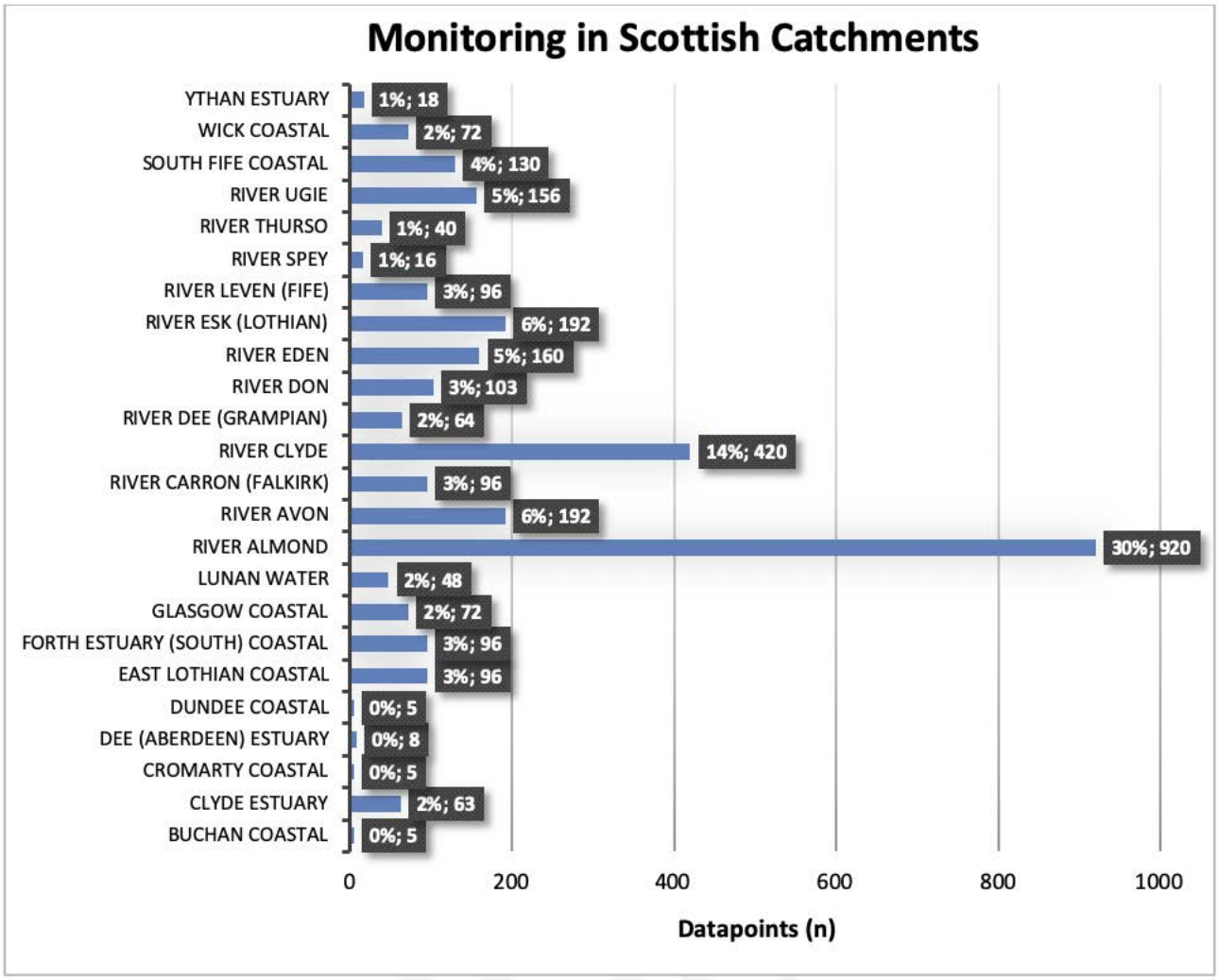

Figure 7 Scottish catchments (24 total) with monitoring data, with number of datapoints and percentage

Gap analysis by catchment

A total of 24 catchments out of the 391 Scottish catchments have been monitored for pharmaceuticals. The largest portion was performed in the River Almond (920 datapoints, 20% of data), River Clyde (420 datapoints, 14% of data) and both the River Esk (Lothian) and River Avon had 192 data points and represented 6% of the database (Figure 6). Little monitoring was performed in the River Thurso (40 datapoints), River Spey (16 datapoints), Ythan estuary (18 datapoints), Dee (Aberdeen) estuary (8 datapoints), Dundee coastal (5 datapoints), Cromarty coastal (5 datapoints) and Buchan coastal (5 datapoints). These catchments each represented ≤1% of the total catchments included in the database.

The five substances of higher risk followed similar trends to the total database, with the most monitoring performed in the River Almond, River Clyde, River Esk (Lothian) and River Avon. However, diclofenac was the only one of the five that was monitored in all 24 of the catchments included in the database. Monitoring data was missing for ibuprofen (River Spey, Ythan estuary), clarithromycin (Buchan coastal, Cromarty coastal, Dundee coastal), erythromycin (Buchan coastal, Cromarty coastal, Dee (Aberdeen) estuary, Dundee coastal, River Thurso, Wick coastal) and 17α-ethinylestradiol (Buchan coastal, Cromarty coastal, Dundee coastal, River Spey, Ythan estuary).

SEPA has appointed fourteen priority catchments (Table 6). It should be noted that these were identified because of concerns about diffuse pollution, so did not focus on WWTW. As they may represent catchments with significant farming activities, they may be a useful starting point for investigating veterinary pharmaceutical pollution. Pharmaceutical monitoring has been performed in the Buchan Coastal, River Ugie and River Dee (Grampian). No pharmaceutical monitoring has been performed in the remaining priority catchments. Additionally, several of the SEPA priority catchments lack data for the substances of higher risk, including those indicated in the table (for all five substances) and Buchan coastal (for clarithromycin, erythromycin, 17α-ethinylestradiol).

Table 7 SEPA Priority Scottish catchments (SEPA, 2020)			
Catchment	**Pharmaceutical Monitoring**	**Catchment**	**Pharmaceutical Monitoring**
River Ayr		Eye Water	
River Doon		River Tay	
River Irvine		River South Esk	
River Garnock		River Dee (Grampian)	X
North Ayrshire Coastal		River Ugie	X
Galloway Coastal		River Deveron	
Stewarty Coastal		Buchan Coastal	X

Gaps by source proximity

WWTWs in Scotland

Scottish Water operates a total of 1,862 WWTWs in Scotland (Figure 7), classified as primary (39 sites, 2%), secondary (483 sites, 26%), tertiary (139 sites, 7%), 'not WIC reportable' (13 sites, 1%), preliminary only (11 sites, 1%) and cess and septic tanks (1,177 sites, 63%). The population equivalent (PE) values - an indication of the capacity of the plant - range from 0 to 754,658 (mean 3651). Private and SEPA-regulated sites are not included in this dataset. WWTWs are present in all 32 Scottish local authorities, and 161 of the 391 Scottish catchments. Gap analysis revealed that pharmaceutical monitoring has occurred in close proximity (within the same catchment) to 440 WWTWs (23% of total Scottish WWTWs). The most pharmaceutical monitoring was performed in West Lothian (containing 22 WWTWs), North Lanarkshire (containing 15 WWTWs) and Aberdeenshire (containing 193 WWTWs) local authorities, and the River Almond (containing 12 WWTWs) and River Clyde (containing 128 WWTWs) catchments. There are WWTWs in the 14 priority catchments listed by SEPA, and 11 of these catchments lack monitoring data.

A comprehensive list of catchments with and without monitoring data, and the presence of WWTWs (number, types and population equivalent), is included in Appendix XI (Tables XI-1, XI-2). Of all Scottish catchments, the River Clyde has the most WWTWs (128 total: 21 secondary treatment, 13 tertiary treatment and 94 septic and cess tanks). The River Tweed catchment has the second most WWTWs in Scotland (78 total: 2 primary treatment, 33 secondary treatment, 8 tertiary treatment and 35 septic and cess tanks). However, no pharmaceutical monitoring has been performed in the River Tweed catchment within the past five years (South Lanarkshire and the Scottish

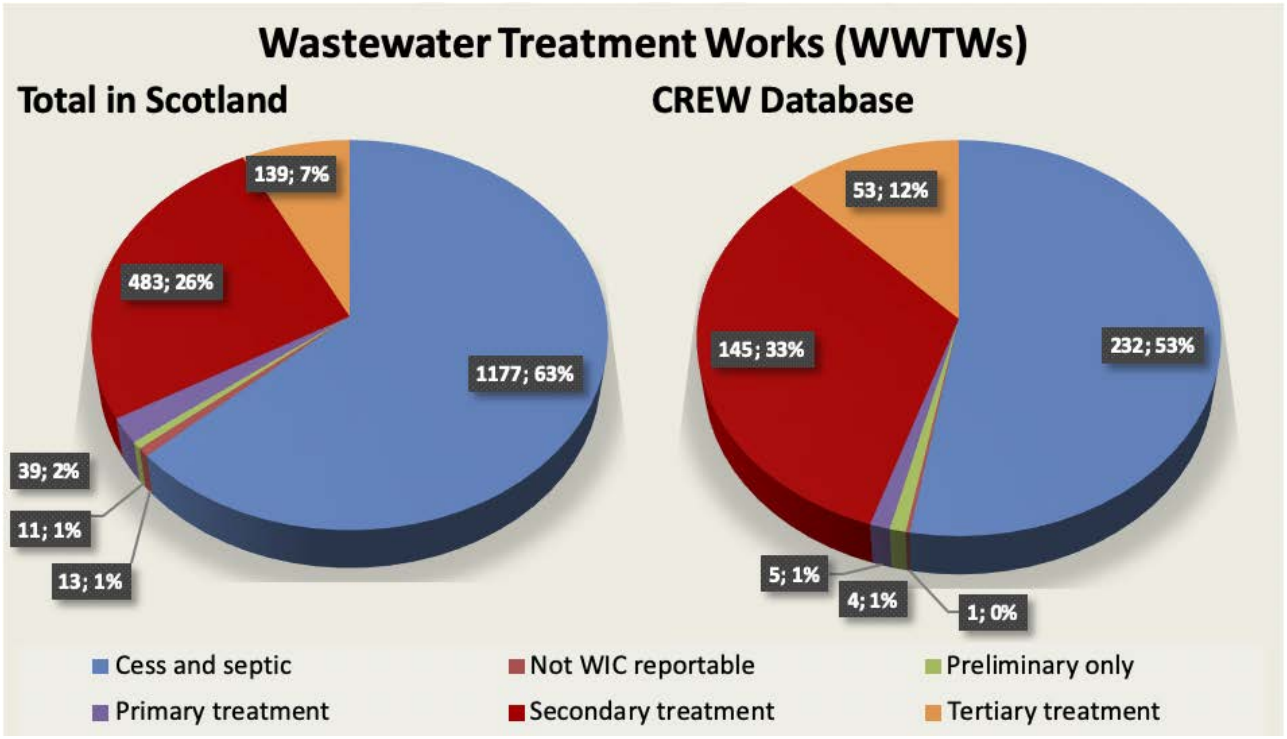

Figure 8 WWTWs by type in Scotland (1,862) compared to those in catchments with monitoring data in the project database (440), with number of datapoints and percentage. WIC = Water Industry Commission.

Borders local authorities). Additionally, no monitoring has been performed in Dumfries and Galloway (179 WWTWs), Na h-Eileanan an Iar (170 WWTWs) and Argyll and Bute (150 WWTWs) local authorities. Limited monitoring has been performed across the Highland region (302 WWTWs total). Only the River Thurso (6 WWTWs), River Spey (18 WWTWs in the Highland region), Wick coastal (14 WWTWs) and Cromarty coastal (21 WWTWs) have been sampled for pharmaceuticals with 59 WWTWs total, accounting for 19% of total WWTWs in the region. Although the Highland local authority has the most WWTWs, this region has the lowest overall population density (8%). However, densely populated towns may be present within this region and, due to tourism, local populations may be subject to seasonal change.

NHS Sites in Scotland

There are 453 NHS sites across Scotland, these have been subdivided into 6 categories: acute hospital (30 total), mental health hospital (28 total), maternity hospital (2 total), multi-service hospital (9 total), patient residential care facility (14 total) and other (370 total) (Figure 8). Average bed numbers range from 0 to 1607 (mean 42). All 32 local authorities (and 95 catchments) have NHS sites. A list of categories, number of beds and location is included in the appendix (Table a2). Gap analysis revealed that pharmaceutical monitoring has occurred in close proximity (within the same catchment) to 182 NHS sites (40% of total). The most pharmaceutical monitoring was performed in West Lothian (containing 10 NHS sites), North Lanarkshire (containing 10 NHS sites) and Aberdeenshire (containing 19 NHS sites) local authorities, and the River Almond (containing 9 NHS sites) and River Clyde (containing 24 NHS sites) catchments. Catchments with monitoring data but no NHS sites include the Clyde estuary, Dee (Aberdeen) estuary and Ythan estuary.

A list of catchments without monitoring data, and the presence of NHS sites (number, categories and number of beds), is included in the appendix (Table a1). Of all Scottish catchments, Glasgow Coastal (39 total; 4 acute, 3 mental health, 32 other), River Clyde (24 total; 2 acute, 2 mental health, 1 multi-service, 19 other) and Dundee Coastal (20 total; 1 acute, 1 mental health, 1 multi-service, 17 other) have the most NHS sites. However, no pharmaceutical monitoring has been performed in the regions of the Glasgow Coastal catchment including Renfrewshire (6 NHS sites) and West Dunbartonshire (4 NHS sites) local authorities, or Dundee Coastal region including Dundee City (16 NHS sites). Additionally, no monitoring has been performed in Dumfries and Galloway (23 NHS sites), Argyll and Bute (12 NHS sites) or East Ayrshire (20 NHS sites) local authorities. Limited monitoring has been performed across the Highland region (with 60 NHS sites total). Only the River Thurso (2 NHS sites), Wick coastal (5 NHS sites), River Spey (7 NHS sites in Highland region) and Cromarty coastal (3 NHS sites) have been sampled for pharmaceuticals, which contain 17 NHS sites total and account for 28% of total NHS sites in the region. The Highland local authority has

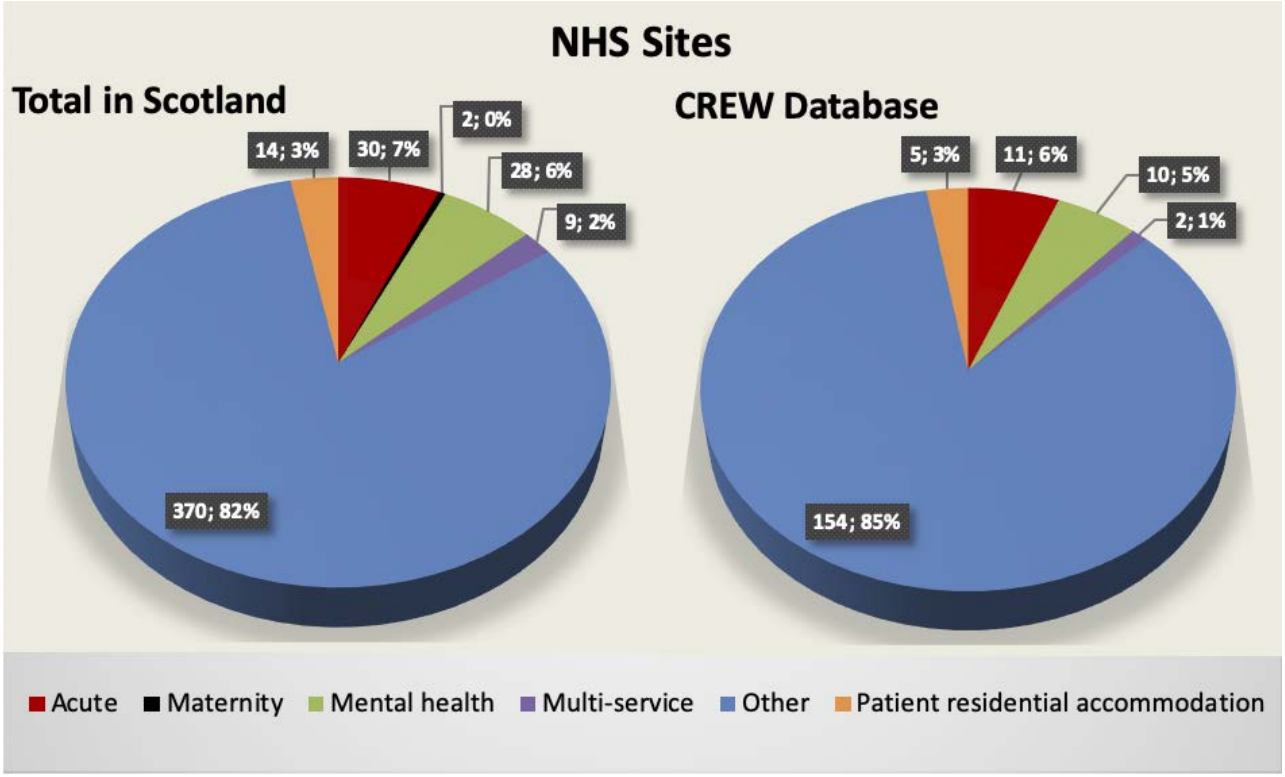

Figure 9 Total NHS sites in Scotland (453) compared to those in catchments with monitoring data in the CREW database (182), with number of datapoints and percentage value, by NHS site category.

the lowest population density total, but variation based on town/city population and source proximity may exist.

3.4 NHS datasets

As environmental monitoring is resource-intensive, predicted environmental concentrations can be a useful way to provide interim risk calculations. This section sets out what NHS datasets may be useful for this purpose in future research.

3.4.1 Introduction

The National Services Scotland (NSS) Information Services Division (ISD), which is part of Public Health Scotland (https://publichealthscotland.scot/our-organisation/about-public-health-scotland/our-vision-and-values/), manages all health service data for NHS Scotland (ISD, 2020a). It provides three datamarts on prescribing activity: PRISMS (community pharmaceutical/medical service dispensing), HMUD (hospital dispensing) and the antimicrobial (AMIDS) datamarts. These are subsets of the complete prescribing and medical service dataset, the Prescribing Information System (PIS) for Scotland. There is currently data on over one billion prescriptions, for which the ISD publishes freely available reports with routine prescribing outputs and analysis on use. These include prescribing statistics on monthly prescribing activity, community pharmacy contractor activity and prescribing practice and dispensing pharmacy data (ISD, 2019). Reports are also published annually which summarise pharmaceutical use by specific therapeutic group or patient condition, such as the *Scottish One Health Antimicrobial Use and Resistance in Humans* report, *Medicine Used in Mental Health* report, *Minor Ailments Service* report and *Prescribing of Smoking Cessation Interventions* report (ISD 2019; ISD, 2020a). The Scottish Antimicrobial Prescribing Group (SAPG) works collaboratively with ISD to publish the report summarising annual antimicrobial use and resistance in humans (ISD, 2020b). The mental health report summarises data on dispensed prescriptions of antipsychotics, antidepressants, attention deficit hyperactivity disorder (ADHD) drugs and dementia drugs (ISD, 2020c). The *Minor Ailment Service* provides information on the number of prescriptions dispensed by local pharmacies for treatment of minor ailments or injuries; this includes fever, allergies, aches and pains, cold and flu symptoms and skin conditions (acne, warts, fungal infections, etc.) (ISD, 2020a; ISD, n.d.). The ISD recently launched a new beta website (https://beta.isdscotland.org/), which contains the most up-to-date reports and publications. The previous ISD website contains earlier publications and will be functional for a continued period of time (unspecified) (https://www.isdscotland.org/Health-Topics/Prescribing-and-Medicines/).

Several other datamarts are available from the ISD but were judged to be not relevant in relation to prescription activity and drug use in Scotland (ISD, 2020d). These include: *Accident and Emergency (A&E2)* reporting on patient attendance in A&E's across Scotland, *Acute Cancer Deaths and Mental Health (ACaDMe)* datamart, *National Theatres Implementation Group (NTIG)* datamart with data on theatre activity, a datamart on *Outpatients (SMR00)* appointments, *Quality Improvement National Reporting Tool for Scotland* (QINRT) which performs assessments on healthcare quality, *Scottish Patients at Risk of Readmission and Admission (SPARRA)* datamart and *Waiting Times* datamart.

3.4.2 Datasets

1 PIS

The Prescribing Information System (PIS) is the complete national prescribing dataset (ISD, 2012)). This dataset includes a large variety of data on prescribing and dispensing at the individual patient level, electronic messaging data (e.g., e-Prescribed and e-Dispensed items) and additional financial items (ISD, 2012). This is a robust dataset, with several pitfalls as it is not straightforward or intended for quick analysis. It requires "advanced analytical skills and experience of prescribing data" for effective investigation and use (ISD, 2012).

Information on the prescriber includes location where prescribing took place (e.g., GP practice, dental practice) with information on the number of patients (e.g., age and gender), and the prescribing individual (e.g., general practice doctor, nurse, dentist) that is assigned a prescriber professional number and information on the prescriber (e.g., year of birth, gender and sub type (e.g., registrar, optometrist, district nurse)) (ISD, 2010). Dispenser location relates to location type (e.g., community pharmacy, dispensing doctor). Patient data includes date of birth, age, gender, and (if applicable), care home residency. Geographical location can relate to location where the prescribing/dispensing took place (at the council, electoral, postcode, Scottish constituency and UK constituency granularity; with urban and rural differentiation), and the patient's home address (ISD, 2010). Geography is also broken into NHS organisation details, with health board name and information included (ISD, 2010). Classes of information are available on prescriptions processed through paper scanning system (e.g., dates, prescribable item details, type and quantities) (ISD, 2010).

2 PRISMS datamart

PRISMS is a subset of the full PIS and is a web-based application for NHS staff which offers information on all prescriptions dispensed in the community (April 2004

– present). Prescriptions are generally written by GPs, although non-medical prescribers such as nurses, dentists and pharmacists may write prescriptions (ISD, 2020e). All data is based on items "dispensed by community pharmacies, dispensing doctors and a small number of specialised appliance suppliers" (ISD, 2020e). PRISMS includes 275 reports on budget, comparison reporting, controlled drug monitoring, cost and volume analysis, generic savings, growth, national therapeutic indicators, prescribing indications, *Quality Outcome Frameworks* (QOF) reports and unscheduled care (ISD, 2020a). This data reports at the individual practice, locality, Community Health Partnership, NHS Board and Scotland level. This datamart is updated monthly, and access is limited to authorised NHS staff.

3 Prescribed & Dispensed

Prescribed & Dispensed is an open access dataset (2016 – present) containing annual data on items prescribed and dispensed in the community at prescribing location (GP practices, dentists and hospitals) and community pharmacies within Scotland (ISD, 2020f). The data is extracted from the PIS database, as prescriptions dispensed in the community and claimed for payment by the pharmacy contractor (e.g., pharmacy, dispensing doctor, appliance supplier). There is no information on private prescriptions or drug consumption/use in accordance with dosage instructions (ISD, 2020f). The data is reported by date, prescriber location, prescriber type where prescription was written (e.g., hospital ward, GP practice, community pharmacy), prescriber type (e.g., pharmacist, dentist, general practitioner, nurse), dispenser location, dispenser location type (e.g., appliance supplier, community pharmacy, dispensing doctor) and number of paid items. The metadata tables (2016 – 2019) are available through the new ISD beta website, on the NSS open data platform in text/csv format (https://www.opendata.nhs.scot/dataset/prescribed-dispensed).

4 Hospital Medicines Utilisation Database (HMUD)

The HMUD allows comparison of medicine use in different hospitals across Scotland, including across different NHS Boards and hospital sites (ISD, 2012). The data is provided by individual hospital stock control systems and is updated monthly and available online (2009 – present). The goal is to provide high level information to NHS staff on the cost and clinical effectiveness on medicines used in hospitals (7). There are multiple datamarts within the HMUD, representative of functional areas (e.g., acute prescribing, cancer-related prescribing, etc.) (ISD, 2012). No patient level information is included in HMUD, and hospital data is reported at individual hospital, NHS Board and (if applicable) cancer network level (ISD, 2012). Comparisons can be performed by approved NHS staff on medicine use in different hospitals and NHS Boards in Scotland.

5 Antimicrobial Management Integrated Database for Scotland (AMIDS)

The AMIDS datamart provides information on antimicrobial use and patterns of antimicrobial resistance in Scotland (Niemi, 2020). It is a web-based application with restricted access. Users are able to "explore the trends between antimicrobial use and the development of antimicrobial resistance and Clostridium difficile infection (CDI)" (Niemi, 2020). Antimicrobial use is collated from the PIS primary care prescribing data, the HMUD secondary care prescribing/activity data and the Electronic Communication Surveillance in Scotland (ECOSS) data on antimicrobial resistance and cases of CDI in humans (ISD, 2020d). The goal of this datamart is to allow NHS boards to improve the quality of antimicrobial prescribing and mitigate AMR development. This datamart is used by the Scottish Antimicrobial Prescribing Group (SAPG) to regulate and improve antimicrobial use (Niemi, 2020). The SAPG publishes the annual *Scottish One Health Antimicrobial Use and Resistance in Humans* report.

6 Prescribing Cost Analysis (PCA)

PCA (2001 – 2016) reports on the number of items and the gross ingredient cost (GIC, to the Scottish Government) of all NHS prescriptions dispensed in the community in Scotland; including those dispensed by community pharmacies, dispensing doctors and specialist appliance suppliers and stoma providers (Scottish Government, 2017). This report is produced annually and includes statistics on volume and cost with drug/device name and individual preparation for Scotland (number of dispensed items, GIC and cost per item) (ISD, 2020a; Scottish Government, 2017). The majority of prescriptions are written by GPs (additionally nurses and dentists), and data includes prescriptions written in hospitals that are dispensed in the community (Scottish Government, 2017). Further statistics are provided on the: top 10 drugs dispensed in Scotland (buy volume, cost and rate of prescribing), and top ten movers of drugs/devices showing the most increase/decrease by number of items dispensed and GIC over the most recent financial year (Scottish Government, 2017). There is 10-year trend data available for generic drug prescribing at the Scotland level, and two-year trend data at the NHS board level (Scottish Government, 2017). A summary statistics table is included in the report which summarises data on the volume and net cost of prescriptions dispensed in Scotland. Report summaries are published in addition to the full PCA.

7 Hospital and NHS site location, size and classification data

The NHS NSS operatives maintain a geo-referenced file of all NHS sites across Scotland (ISD, 2017). This is in addition to the postal address list of hospitals and other NHS sites that is openly available on the NHS website. Classification of hospitals by type, and indication of size by number of beds, is present in the *Hospital Sector Running Costs* national finance report (ISD, 2017). These files are available online and can be downloaded in the detailed tables R020 and R020LS, https://www.isdscotland.org/Health-Topics/Finance/Costs/Detailed-Tables/.

4.0 Discussion

Results and gap analysis

Analysis of the results indicates that many pharmaceuticals are ubiquitous. The project selected 5 compounds for mapping ecotoxicological risk - ibuprofen, clarithromycin, erythromycin, EE2, and diclofenac – and identified a further three – propranolol, ranitidine and metformin - that also had relatively high detection frequencies and risk bands. Clarithromycin, erythromycin and ciprofloxacin posed the highest risk in terms of AMR and were also taken forward for mapping, . In total 9 compounds were highlighted. However, this short list should not be seen as a definitive 'priority list', as it should be noted that some compounds were targeted for analysis over others and that some compounds have never been analysed in Scotland. 'Missing' compounds include a number of antipsychotics (flupenthixol, haloperidol and risperidone) and a range of antibiotics – the macrolide roxithromycin, tetracycline, and several penicillins. The latter are known to degrade due to an unstable beta-lactam ring but include some of the most commonly used medicines in Scotland, in particular amoxicillin and flucloxacillin. Piperacillin is usually given by injection and mostly used in hospitals (Helwig et al., 2016) and could lead to 'hotspots' where hospital effluent is discharged.

Whilst WWTW influent and effluent were well-sampled, there is little or no data on other potential sources, such as septic tanks, manufacturing effluent, landfill effluent, veterinary sources, aquaculture, and run-off from fields to which sewage sludge was applied. Most WFD water body types, other than rivers and burns, were also underrepresented.

Geographically, sampling results were available for only about half of Scotland's local authority areas, and visual analysis of the map clearly shows that large areas are underrepresented. Other possible analyses, which were not part of this project, could include whether data exists for environmentally sensitive water bodies, whether rivers are represented by size (e.g. based on flow) or whether water bodies under pressure from potential sources other than hospitals and WWTW have been investigated.

Towards a change in formulary

The purpose of the project was to establish a baseline on pharmaceutical pollution in the Scottish aquatic environment, rather than to establish which pharmaceuticals should be targeted for intervention. An overall 'priority list' is of limited use when considering alternatives for prescribing purposes, as less harmful substitutes need to be available within a certain therapeutic group (unless non-pharmaceutical interventions are an option).

An important consideration is whether current environmental risk is the most appropriate parameter to consider when preparing a formulary update with the purpose to reduce overall environmental risk from pharmaceuticals. Risk depends on both prescription volume and on toxicity, and it may be that a more toxic compound carries a lower risk due to a lower prescription volume. If a formulary update recommends a shift towards the lower risk, but higher toxicity compound, then in the longer term the environmental toxicity may increase due to a 'transferral' of risk from one compound to another. This can lead to what is sometimes referred to as "regrettable substitutions"; for example, Bisphenol S (BPS), a replacement of the problematic plasticiser Bisphenol A (BPA), has been now found to be as oestrogenic as BPA, as toxic to embryos as BPA, and even more persistent in the environment (Trasande, 2017). Hazard, on the other hand, is an indicator of the intrinsic harmfulness of a compound, but does not take into account current usage or, therefore, current risk. Factors such as drug metabolism and removal in WWTW also come into play.

To illustrate this, we draw on a study by the Institute for Health and the Environment (RIVM) in the Netherlands, in which key stakeholders (Minister of Health, insurers, prescribers, etc.) were interviewed about their willingness to implement changes to prescribing. The interviewers used 'paired drugs' as examples (e.g. diclofenac vs. naproxen/ibuprofen) and also included Cognitive Behavioural Therapy *vs.* fluoxetine as a pair. The outcome was that although the willingness to change was high, there are still a lot of questions over what is environmentally preferable. For example, in Table 7, which is adapted from their report, Defined Daily Dose (DDD), % excreted unchanged, removal in WWTW and 'safe concentration' are listed for the three NSAIDs.

Table 8 Comparison of risk from NSAIDs (adapted from Van der Grinten et al., 2017). It should be noted that the risk value here is not RQ, as dilution is not taken into account; the values serve only to enable comparison between the compounds.

	DDD (mg)	% excreted unchanged)	% removed in WWTW	safe limit (µg/L)	Emission into surface water per patient per day (mg)	Comparative risk (emission/safe limit)
Diclofenac	100	16	29±23	0.1	1136	113.6
Naproxen	500	10	84±23	1.7	8	4.706
Ibuprofen	1200	30	96±5	0.01	14.4	1440

Based on DDD, excretion and removal, the emission per patient is not hugely different (only a factor 1.8). While the comparative risk for naproxen works out the lowest, the safe limit, meanwhile, is based on different ecotoxicity tests. The toxicity for diclofenac was established based on a test for impact on gills and kidneys of fish, while the safe limit for ibuprofen was based on a study involving embryos. The RIVM study explains that tests have not been carried out with the other two drugs, so that the most sensitive endpoints for ibuprofen and diclofenac were not investigated in the same way for naproxen. Moreover, the toxicities for both ibuprofen and diclofenac are disputed by the industry (Van der Grinten et al., 2017), which could lead to a change in the assessment. The stakeholders in the study indicated that recommendations for changes to prescribing need to be very robust, or they will undermine confidence in future decisions and the overall recommendation of the report is that a robust assessment framework is developed to guide decision-making.

Visualisation

In October 2019, an interim report was presented to the Steering Group with suggestions for visualisation. Three distinct proposals were offered: a 3-D visualisation style, a dashboard style, and an interactive GIS map. At the request of the Steering Group, only the interactive GIS map was taken forward for further development, which resulted in the maps included as Appendices IV-VI.

When communicating risk, it is important to consider what exactly the objectives of doing so are. Different audiences have different skillsets, knowledge and understanding and levels of interest. The risk message may be conveyed in order to inform, or in order to drive behaviour change.

Whilst we expect OHBP members are an important audience for the outputs from this project and are skilled in the use of interactive maps, it cannot be assumed that all audiences have the ability and interest to access map-based information. A wider range of other visualisations might need be considered for other audiences, such as prescribers or the general public, such as dashboard-style risk class information, pictograms or other illustrations, locally-specific information, interactive (virtual reality) information, depending on the audience, the message, and the purpose of communication.

Database maintenance

A table to track data supplied by the project partners was set up and each data set received was recorded along with supporting information. The project data is stored in a secure network location at the James Hutton Institute which is backed up as part of routine system administration.

A metadata form was produced to record information on the datasets used in the project. This form was designed to achieve compliance with the INSPIRE (Scotland) Regulations 2009.

5.0 Recommendations pertaining to the project objectives

Monitoring data availability and gap filling

The first objective of the project was to assess the spatial and temporal availability of baseline data in Scotland and to identify gaps in the available datasets. The third objective was to make recommendations for small-scale gap filling.

With regard to these objectives, we recommend that:

1. A targeted monitoring campaign is conducted for all substances highlighted in section 3.3.1 – those pharmaceuticals that have never been targeted for analysis in the Scottish environment. If resources are limited, these can be prioritised through a desktop study of consumption, excretion, removal in WWTW and ecotoxicological / AMR thresholds. It would furthermore be beneficial to engage a clinician to understand which patient groups receive these substances (for example, haloperidol is highly prescribed in (some) care homes) in order to select appropriate locations for monitoring.
2. A risk-based approach, based on population density

and available dilution, is adopted to fill the spatial gaps, as no monitoring has taken place in substantial parts of Scotland. Whilst it is acknowledged that the CIP2 Scotland project investigated WWTW with low available dilution, urban regions such as Aberdeen City, Dundee City, Dunbartonshire (East and West) and Renfrewshire, which have both high population and population density, have little or no monitoring data, and cumulative risks from multiple WWTW may exist.

3. The lack of representative monitoring data from the rural regions on the mainland is addressed. While rural areas such as these may have low population density across the entire local authority, densely populated towns or cities may be present within the region and WWTW infrastructure may be less sophisticated than in urban areas. Fluctuations in population e.g. due to tourism should also be taken into account.

4. Further monitoring of the substances of higher concern is carried out in all surface water types other than rivers and burns, as well as in ground water. Of the five substances of higher risk, only ibuprofen and diclofenac were monitored in estuarine surface water, and only very limited monitoring for these compounds has been performed in lochs.

5. The cumulative impacts of septic tanks are investigated in areas with high private septic tank density and low dilution. Only one study on septic tanks, targeting a limited range of substances, was available.

6. More detailed spatial analysis is undertaken about the inclusion of sampling sites in relation to WWTW that receive hospital effluent. The current project was only able to do that based on catchments in which the NHS estate is located, which is of limited value due to the size of catchments.

Risk Evaluation

The second objective of the project was to identify threshold values for ecotoxicity and selection for antimicrobial resistance (AMR) (where appropriate) and to evaluate environmental concentrations of pharmaceuticals against these.

With regard to ecotoxicity, we recommend that:

7. The PNEC database is expanded and consolidated, by dedicating more time to the collation and evaluation of ecotoxicity studies. This work is not Scotland-specific and should be considered for a joint project with other (international) partners, such as the Wikipharma database (http://www.wikipharma.org/welcome.asp) team or the NORMAN network (https://www.norman-network.com/)

8. Further ecotoxicity studies are conducted for substances for which ecotoxicity data is lacking or insufficient (in particular for substances highlighted in the gap analysis), in line with the objective for filling remaining knowledge gaps adopted in the EU's Strategic Approach to Pharmaceuticals in the Environment, which specifically refers to pharmaceuticals brought to market prior to the inclusion of a requirement for Environmental Risk Assessment in the authorisation process.

9. Risk threshold information is gathered not just for compounds of the highest risk, which have usually been the focus of ecotoxicity studies, but also for those substances considered as alternatives, in order to avoid "regrettable substitutions".

With regard to AMR risks, we recommend that:

10. The occurrence of ARGs, as well as the relationship between the presence of antibiotics and AMR in WWTW, effluents and rivers downstream from WWTW, is investigated. More than 100 measurements of antibiotics in influents and effluents resulted in RQ(AMR) > 1. It is likely that the mechanisms that cause antibiotics to drive selection for resistance apply in any environmental matrix, so this is a potential concern.

11. The presence of ciprofloxacin in sludge is investigated, where it may pose a risk when applied to agricultural land. Based on the risk levels established, ciprofloxacin appears to be reasonably well removed by WWTW from the aquatic phase, suggesting that it may transfer to sludge.

12. Further research is carried out to establish whether non-antibiotic pharmaceuticals with antibacterial properties play a role in driving the proliferation of ARGs.

Visualisation of this and future datasets

The fourth objective of the project was to provide initial recommendation on visualising the baseline dataset.

With regard to this objective, we recommend:

13. The use of interactive online maps (as for example at http://waders.hutton.ac.uk/), for easier evaluation of the data. This would be preferable to the current PDF format.

14. Investigating linking or pairing the upstream and downstream measurements, for example by producing a single composite symbol for large scale maps that depicts both the upstream and downstream risk. This would address the fact that currently the

downstream symbols obscure the lower risk upstream symbols.

15. That further consideration should be given to the intended audience, the message to be conveyed, and the purpose of the message (e.g. to inform, or to engender behaviour change), to enable a decision on the most appropriate type of visualisation and other communications.

Following this report, the One Health Breakthrough Partnership has developed a visualisation tool, which provides a graphical representation of the available data on pharmaceutical levels found in Scottish waters, alongside the publicly available prescription data. This will be updated on an ongoing basis with the latest information. The tool will be published by SEPA in early 2022.

6.0 Further recommendations

The insights gained from the literature review, consideration of the datasets, and discussions amongst the research team during the implementation of this project lead us to a number of further recommendations.

Strategic direction

Given that the background to this project was a consideration of a change in formulary towards 'greener' pharmaceuticals, we recommend that:

16. The level of pharmaceuticals identified in this report for Scotland's surface waters raises a concern and should drive policy development to address the issue.
17. A comprehensive strategy to address the risks posed by pharmaceuticals in the water environment should be developed for Scotland.
18. This work needs to be put in the context of a wider approach towards sustainability in Scotland, which may consider potential impacts to Scotland's water, land and air environment, and can include issues such as pollutants, carbon management and AMR.
19. Such a strategy might include a framework for comparative evaluation of substances. There may well be international interest in developing such a framework and it is suggested this could be part of a larger, international project.
20. The frequency or regularity with which formulary updates can be re-issued in Scotland is considered, as discussed in section 4.0. If regular updates are envisaged, as occurs in the annual revision of the WISE list, then risk (RQ) is a sensible basis for comparison. If not, a 'Compound Hazard Indicator' could be developed, based on toxicity, excretion, metabolite toxicity, persistence, removability in WWTW, fate in the environment, and potential to bio-accumulate. Such an indicator would capture environmentally relevant factors but not be affected by a change in prescription behaviour, so the hazard assessment would remain valid.
21. Ecology expertise is sought to gain a better understanding of the resilience of ecosystems under the influence of seasonal variation in concentrations, such as under drought conditions when less dilution is available. For most of the substances of higher risk, mean values are medium to high, suggesting that risk thresholds may be breached during dryer periods . If longer-term adverse effects occur during such periods, mean values may not offer sufficient protection.

Non-WWTW and veterinary sources

Whilst it is commonly assumed that WWTW are the main source of pharmaceutical pollution, little research has been done on source attribution and regional differences may exist. It is recommended that:

22. Landfill sites, pharmaceutical manufacturing sites, veterinary sources and aquaculture are investigated as potential sources of pharmaceutical pollution, to complete our understanding and inform future modelling work. Aside from environmental monitoring, stakeholder interviews on the specific substances used and on management practices affecting patterns of discharge could be valuable, as could more detailed spatial analysis of the current database (by adding layers representing other potential sources) to establish to what extent sampling in proximity to other sources is already included.

Use of modelling and further spatial analysis

Given that sampling and analysis is resource-intensive, spatial modelling can be used in conjunction with environmental monitoring. Several such models exist. It is recommended that:

23. A review of existing modelling approaches to predicting environmental pharmaceutical concentrations is undertaken, with a view to adopting one in Scotland to inform and validate continued policy development on this issue.
24. Risk prediction utilises NHS datasets (if possible through automated analysis) and is updated regularly,

if possible in collaboration with Scottish Water so that data can be combined with sewer and WWTW infrastructure.

25. Further GIS analysis of the existing dataset is employed to gain a better understanding of relationships between potential sources of pharmaceuticals and measured concentrations downstream, taking into account cumulative sources, for the substances highlighted in this project as a minimum .

Future maintenance of the database and partnership working

Finally, this project was the result of a unique partnership which enabled the collation of available data and gap analysis on a national scale. It is therefore recommended that:

26. The strategic collaboration between industry, regulator and research institutions is continued and the project database maintained as a permanent, secure, shared database, using the change tracker provided to enable longer-term monitoring and management of pharmaceutical concentrations in the environment. It is recommended that the partnership consider appointing a database custodian.

27. If multiple institutions agree to contribute their future work to a central database, it would be beneficial to agree to a greater degree the protocols of sampling and analysis, to enhance comparability.

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CREW is a partnership between the James Hutton Institute and all Scottish Higher Education Institutes and Research Institutes. The Centre is funded by the Scottish Government.