

Investigation of the Implications for Ireland of Emerging Standards on Pharmaceuticals in Receiving Waters

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EPA Research Programme 2014–2020

**Investigation of the Implications for Ireland
of Emerging Standards on Pharmaceuticals in
Receiving Waters**

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by

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Executive Summary

Water is essential for all human activities. Drinking and food preparation, support of the natural environment and a growing economy all require a healthy and secure water supply. Unfortunately, there are significant pressures on this fragile resource. To ensure both the preservation of healthy waters and the restoration of unhealthy waters, it is critical that such harmful pressures be addressed by researchers. The aim of this project was, therefore, to provide a baseline study investigating pollution of Irish waters with three potentially hazardous pharmaceutical compounds: diclofenac, 17-beta-estradiol, and 17-alpha-ethinylestradiol.

Pharmaceutically active chemicals (PhACs) include the active ingredients in pharmaceuticals and their metabolites/transformation products. These pollutants most commonly enter waterways from the human use of medications, followed by their excretion and incomplete removal at municipal wastewater treatment plants (WWTPs). There is increasing concern about the continuous release of PhACs into the aquatic environment. The Water Framework Directive (WFD) – the main piece of European legislation for protecting and improving water quality – has, therefore, put forward new legislation. In accordance with Article 8(b) of Directive 2013/39/EU, diclofenac (an anti-inflammatory drug), 17-beta-estradiol (E2) and 17-alpha-ethinylestradiol (EE2) (a natural and synthetic oestrogenic hormone) have been added to a so-called “watch list”. These three PhACs will receive EU-wide monitoring, which will determine whether or not they are added to the priority substances listed by the WFD. This 1-year desk study investigated the implications for Ireland of the addition of these three PhACs to the priority substances list.

First, a comprehensive systematic literature review was conducted to evaluate the current state of European knowledge on these three PhACs. After screening 3952 potentially relevant articles, an EU-wide database of 1268 publications on diclofenac, E2 and EE2 was created. A bibliographic analysis (an analysis of published research) of the publications in the database revealed that water-related research on these compounds has increased steadily from 1995 to 2015. The literature review found that European surface water concentrations of diclofenac are typically below the

proposed environmental quality standard of 100 ng/L, but that these limits are occasionally exceeded. E2 and EE2 surface water concentrations are typically below 50 ng/L and 10 ng/L, respectively, but these values greatly exceed the proposed environmental quality standards (EQSs) for these compounds (0.04 and 0.035 ng/L, respectively). However, only 21 publications in this database were contributed by Ireland, implying that greater monitoring of Irish receiving waters is required in the future for improved risk management and decision-making. Most importantly, while current laboratory-based analytical chemistry methods are sufficiently sensitive for the detection and quantification of diclofenac, methods with increased sensitivity are required for E2 and EE2.

Next, in order to evaluate the mobility of these PhACs in an Irish context, existing Irish data were collated and used to map monitoring locations, frequency and, where possible, concentrations of the compounds that exceed proposed EQSs. This novel mapping exercise revealed that, based on the data extracted from the literature and mapped in this report, the majority of Irish surface waters do not exceed WFD proposed EQS values for diclofenac, E2 and EE2, but that point sources of pollution could lead to occasional hotspots that exceed these limits. These predictions, however, are based upon the use of very limited data and are especially uncertain for the oestrogens because of the problems associated with detecting such low concentrations of these compounds. There is a pressing need to develop alternative ultratrace-validated detection methods, such as passive sampling, to report effectively on annual average environmental quality standards (AA EQS) for WFD compliance of monitored receiving waters.

In agreement with national standards, this project also created the first Irish-specific, semi-quantitative risk assessment model for identifying WWTPs that pose high environmental risks arising from these PhACs. A case study was carried out to evaluate this model and potential improvements suggested. Future developments of the model could allow further benchmarking with national and European risk assessment standards.

Finally, an easily digestible toolkit was created for the implementation of control measures at WWTPs with

regard to the PhACs of interest. This work concluded that diclofenac is resistant to conventional wastewater treatment, while E2 and EE2 have high removal rates as a result of biodegradation or sorption to organic matter. The effectiveness of advanced treatments was discussed; however, the most recent literature indicates that the environmental benefits of these treatments may not outweigh their costs.

Overall, this report provides an understanding of the state of research on diclofenac, E2 and EE2 in aquatic matrices in Europe and nationally. It demonstrates that more Irish monitoring data on PhACs are needed, and stresses the importance of preventing the contamination of waterways with this harmful class of emerging pollutants.

1 Introduction

1.1 Project Background

1.1.1 *Water quality management in Ireland*

The Water Framework Directive (WFD; 2000/60/EC) and Irish river basin management plans (RBMPs) establish both legal and operational frameworks to protect and restore clean water and to ensure its long-term, sustainable use. These goals require an integrated approach to the sustainable management and protection of water resources. While Irish ground and surface waters are among those with the highest quality in Europe, the national water assessment for 2010–2012 revealed that there are many impacts that need to be addressed to bring all waters to a satisfactory level and to protect those waters already in a good condition (Bradley *et al.*, 2015). Critical shortfalls in existing Irish RBMPs highlight the importance of affordability and prioritisation considerations, particularly given the economic and social value of a clean and protected water supply. As a result, there is pressing need to ascertain the fate and behaviour of pollutants, along with risk assessing impacts from other complex pressures on these contaminants. Such efforts will contribute to effective decision-making and help ensure a safe and secure supply of drinking water (DECLG, 2015).

1.1.2 *Pharmaceutically active chemicals in the aquatic environment*

Pharmaceuticals are widely used in human and veterinary medicine. Nevertheless, when unintentionally released into the environment, pharmaceuticals can also be a class of pollutants (Fent *et al.*, 2006; Nikolaou *et al.*, 2007). From here on, this class of compounds will be collectively referred to as pharmaceutically active chemicals (PhACs); this term includes pharmaceutically active metabolites/transformation products (Heberer, 2002). PhACs are typically polar, complex molecules developed and used for specific biological purposes (Kümmerer, 2009; Fatta-Kassinos *et al.*, 2011). They are essential to modern healthcare, especially in the developed world, but there are growing concerns about the negative impacts that may result from continuous contamination of the environment with PhACs.

In particular, contamination of the aquatic environment with PhACs has recently been a popular research topic because of the potential toxic effects for aquatic organisms and human health resulting from continuous exposure to these compounds (Fent *et al.*, 2006; Nikolaou *et al.*, 2007; Kümmerer, 2009). Water is essential for all life, and so the protection of this resource is of the utmost importance. The contamination of Irish waters with PhACs is of considerable concern, evidenced by the mention of this issue in the recently released Department of the Environment, Community and Local Government document “Significant Water Management Issues in Ireland” (DECLG, 2015). Specific characteristics of this class of environmental contaminants can, however, present significant challenges for research. For example, PhACs exhibit wide variation in function, chemical structure and physiochemical properties, making it difficult to generalise about their behaviour, persistence or impact in the environment. PhACs are also designed to be biologically active, have a specific mode of action and persist in the body; as a result they can affect humans and wildlife at trace concentrations that are often hard to detect using traditional methods.

PhACs mainly enter the aquatic environment from excretion by humans, followed by incomplete removal at municipal wastewater treatment plants (WWTPs), also known as wastewater agglomerations or sewage treatment plants (Fent *et al.*, 2006; Nikolaou *et al.*, 2007; Zhou *et al.*, 2009). Municipal WWTPs are designed to remove easily biodegradable carbon, nitrogen and phosphorus compounds, but not trace concentrations of PhACs; therefore, these compounds are ultimately released at low concentrations into water bodies that receive treated wastewater (i.e. receiving waters) (Verlicchi *et al.*, 2012). Nevertheless, there are many, non-mutually exclusive, additional pathways of PhACs into the aquatic environment including manufacturer and landfill leachates, hospital wastewater, disposal of unused medicines, agricultural runoff or soil leaching, application in aquaculture and runoff from the spreading of sewage sludge or manure to fields (Fent *et al.*, 2006; Nikolaou *et al.*, 2007; Kümmerer, 2010).

A large number of PhACs have been detected in WWTP influents and effluents and surface, ground and drinking water worldwide in recent years (Ternes, 1998; Heberer, 2002; Nikolaou *et al.*, 2007; Zhou *et al.*, 2009). In fact, it is now established that, throughout surface waters in the developed world, PhACs are present at µg to ng per litre levels (Nikolaou *et al.*, 2007), although the concentrations of specific compounds depend on usage patterns in different countries and can vary with time (Verlicchi *et al.*, 2012). Pharmaceutical loading in the aquatic environment is also expected to increase in the coming years; this is due to an increase in both the mean age of the population and in living standards worldwide, two factors that will likely lead to an overall increase in pharmaceutical consumption (Kümmerer, 2010). The impacts of chronic exposure to trace concentrations of many PhACs on wildlife and human health may be severe; therefore, it is critical to limit as much as possible the concentrations of this class of contaminants in our waterways.

Certain PhACs can specifically impact the endocrine system of humans or wildlife; such chemicals are part of a larger classification of emerging pollutants known as endocrine disrupting chemicals (EDCs). There is concern that chronic exposure to EDCs (in bathing or drinking water, for example) may be linked to adverse human health conditions, such as declining male fertility, birth defects, and breast and testicular cancer (Nikolaou *et al.*, 2007). Furthermore, negative impacts of EDC exposure on wildlife may include severe consequences such as feminisation in fish (Sumpter and Johnson, 2008). Similarly to other PhACs, EDCs often enter the aquatic environment as a result of incomplete removal at WWTPs (Nikolaou *et al.*, 2007).

1.1.3 Legislation underpinning project

Until recently, environmental regulations worldwide had not required explicit testing for any PhACs in water bodies. However, given the growing concern about contamination of the aquatic environment with these compounds, legislation has recently begun to acknowledge this potential problem.

Certain chemicals identified by Annex X of the WFD have been deemed priority substances; these chemicals must be monitored by all EU Member States and cannot exceed specific limits [defined by the legislation as environmental quality standards (EQSs)]. Furthermore, Article 16(4) of this legislation requires

that the list of priority substances be reviewed and adjusted as appropriate at regular intervals. Directive 2013/39/EU of 12 August 2013 added a further 12 substances to Annex X of the WFD. In addition, Article 8(b) of Directive 2013/39/EU states that “the Commission shall establish a watch list of substances for which Union-wide monitoring data are to be gathered for the purpose of supporting future prioritisation exercises.” In response to growing EU concern about the release of untreated PhACs into the aquatic environment, three compounds have been included in the first watch list: diclofenac [2-((2,6-dichlorophenyl)amino)benzeneacetic acid (CAS No. 15307-79-6)] (DrugBank, 2015), 17-beta-estradiol [(17beta)-estra-1,3,5(10)-triene-3,17-diol (CAS No. 50-28-2), hereafter referred to as E2] and 17-alpha-ethinylestradiol [(17-ethinyl-3,17-estradiol (CAS No. 57-63-6), hereafter referred to as EE2]. The EU-wide monitoring data that will be produced in the next few years will help legislators determine whether or not these compounds are ultimately added to the list of priority substances from Annex X of the WFD.

1.1.4 Diclofenac, 17-beta-estradiol (E2) and 17-alpha-ethinylestradiol (EE2)

Diclofenac has one of the highest levels of consumption of non-steroidal anti-inflammatory drugs (NSAIDs) in Europe (Ferrari *et al.*, 2003; Strenn *et al.*, 2004; Zhang *et al.*, 2008). Diclofenac is used to reduce inflammation and pain for conditions such as arthritis, acute injury, menstrual pain, etc. It is mainly administered orally (accounting for 70% of worldwide diclofenac sales in 2007), but can also be applied as a topical ointment (Zhang *et al.*, 2008). From an environmental perspective, diclofenac is of particular concern because of its direct link to declines in vulture populations in India and Pakistan in 2004; consumption of diclofenac residues led to renal failure in these bird species, which had a severe knock-on effect for whole ecosystems (Oaks *et al.*, 2004). This analgesic drug has also been found to negatively impact male Japanese medaka (fish) (Hong *et al.*, 2007).

17-beta-estradiol (E2) is a natural steroidal oestrogenic hormone. It is produced by men and women, although daily excretion amounts are highest in females, particularly when pregnant (Johnson *et al.*, 2000). Natural oestrogens, including E2, can also be used in prescription drugs or can be derived from animals (Caldwell *et al.*, 2010). 17-alpha-ethinylestradiol (EE2) is a synthetic

oestrogenic hormone; structurally, it is more similar to E2 than any other naturally occurring steroid oestrogen (Wise *et al.*, 2011). Synthetic oestrogens, including EE2, are often active ingredients in oral contraception and hormone replacement therapy drugs (Birkett and Lester, 2003; Wise *et al.*, 2011). Overall research suggests a link between environmentally relevant levels of these steroid oestrogens and negative effects on many wildlife species (Kunz *et al.*, 2015).

1.2 Project Objectives

With legislation for regulating levels of diclofenac, E2 and EE2 pending, studies in an Irish context are necessary to ensure national compliance with upcoming European standards. The aim of this project was to provide a baseline study for Ireland with regard to the implications of the potential addition of diclofenac, E2 and EE2 to the EU priority substances list. A number of key technical objectives were identified:

- review the current national and EU state of knowledge on sources, receptors, monitoring and control measures for the compounds of interest;
- compile relevant existing Irish data on environmental concentrations of the compounds of interest;
- map monitoring efforts and data for the compounds of interest and factors impacting their distribution/concentration in Ireland, to evaluate their mobility in an Irish context;

- provide a preliminary risk assessment (RA) for Irish urban WWTP effluents with regard to compounds of interest and review necessary and missing data for future RA efforts;
- create a toolkit to assess control measures for compounds of interest; and
- create an EU-wide database for future data collection/information gathering.

1.3 Structure of the Report

This synthesis report is organised into four main sections: an introduction (Chapter 1), a summary of the methods and results of each of the main work packages (Chapter 2), a summary of the main conclusions and suggestions for future research (Chapter 3) and policy recommendations (Chapter 4). The report included four main work packages: (1) a comprehensive systematic literature review and bibliographic analysis for diclofenac, E2 and EE2 research; (2) a review and Geographic Information Systems (GIS) mapping of existing national monitoring data; (3) a novel, semi-quantitative, environmental RA for evaluating the threat posed by Irish WWTP discharges with regard to these PhACs; and (4) a review of control measures that reduce levels of these three compounds in the aquatic environment. This report provides a summary of the work, but a more detailed description can be found in the Final Technical Report for this project.

2 Summary of Work Package Methods and Results

2.1 Work Package 1: Systematic Literature Review and Bibliographic Analysis

2.1.1 *Work package 1 aim and research questions*

The overall aim of work package 1, the literature review, was to identify and evaluate all previous relevant national and EU-wide studies on contamination of the aquatic environment with three PhACs on the European monitoring list (the “watch list”): diclofenac, E2 and EE2. This review is directed towards at-risk industries, companies and sectors that would be affected by the addition of these compounds to future iterations of the WFD priority substance list. It addresses four main research questions for each compound:

1. What are the likely sources/entry points of these PhACs into the aquatic environment?
2. What are the likely receptors and concentrations in European waters?
3. What monitoring methods are currently employed to measure aquatic concentrations of these PhACs, and what are the current limits of detection/quantification?
4. What control measures are effective and employed for lowering concentrations of these compounds in the aquatic environment?

This review does not specifically address the impact of diclofenac, E2 and EE2 on aquatic or terrestrial biota or on human health, because these topics have been addressed fully in previous works (Oaks *et al.*, 2004; Brennan *et al.*, 2006; Hong *et al.*, 2007; McGee *et al.*, 2012). Finally, this review aims to evaluate the state of European research on diclofenac, E2 and EE2 through a bibliographic analysis of the literature on these three PhACs.

2.1.2 *Protocol for systematic review and bibliographic analysis*

Even a cursory search of the literature reveals a vast amount of published material regarding the sources, receptors, monitoring and control measures of diclofenac, E2 and EE2 (Fatta-Kassinos *et al.*, 2011; Johnson *et al.*, 2013; Qian *et al.*, 2015). As a result, this literature review was carried out using a systematic approach. As opposed to a conventional or narrative review, a systematic approach tests a hypothesis or answers a research question based on the published evidence, which is gathered using a predefined protocol (Pullin and Stewart, 2006; Pautasso, 2013). This approach is particularly useful because it helps to avoid bias; when there is too much published information for a conventional review to cover completely, a systematic approach defines a protocol for deciding which studies will be included (Pautasso, 2013).

The systematic review approach utilised by the project team allowed this project to produce a database of publications on the sources, receptors/monitoring and control measures for diclofenac, E2 and EE2. This database was utilised to answer the research questions outlined above. The project’s remaining work packages, the GIS modelling work package (section 2.2), RA work package (section 2.3) and the analysis of control measures work package (section 2.4), all utilised the database as a source of unbiased publications on the PhACs of interest. The database also exists as an independent output from this project, and can be searched for specific topics by keyword, year, or study type. Finally, this systematic approach and database allowed the project team to perform a bibliographic analysis of the literature on diclofenac, E2 and EE2. This type of study summarises the state of European knowledge regarding the PhACs of interest; it allows for the identification of countries/institutes leading in each research topic; and it helps identify knowledge gaps to guide future research (Qian *et al.*, 2015).

The systematic literature review protocol was adapted from the Centre for Evidence-Based Conservation's "Guidelines for Systematic Review in Conservation and Environmental Management" (Pullin and Stewart, 2006). The protocol was comprised of a series of defined steps, designed to identify articles for inclusion in the final publication database and bibliographic analysis. These steps included: (1) defining search parameters (databases to be searched, search times, types of publications included, etc.); (2) selecting search terms; (3) developing eligibility (inclusion/exclusion) criteria; and (4) conducting the literature search and carrying out the article review and selection process. Relevant studies were identified using the Scopus database in May 2015. Search terms were selected to ensure that all potentially relevant articles were returned from the database searches, and two separate searches were run: one for diclofenac and one combined search for E2 and EE2. Only peer-reviewed articles, or review papers published from 1995 onwards were included.

The article review was a two-step process including both a title and abstract filter (see Figure 2.1). The title and abstract review were undertaken by two trained researchers, with 10% overlap in order to validate consistent choices. The final publication database includes bibliographic information about articles that were deemed eligible after the review process. The database also contains additional variables for each article which were defined and determined by the project team during the abstract review. First, the reviewer determined whether the article contained information on the source, receptor/monitoring techniques and/or control measures for one of the compounds of interest (these fields were not mutually exclusive). Second, the article was classified as a chemical or effect-based study; articles could also be classified as both. In contrast to traditional studies that measure the concentrations of compounds in water, effect-based studies can be used to calculate/estimate concentrations of particular compounds in an environmental matrix based on biological effects observed in target organisms (Kunz *et al.*, 2015). Third, the reviewer determined which of the compounds of interest was studied and whether additional chemicals were also included in the study. Fourth, the analytical method employed for detection was noted. Fifth, the type of study was determined (each article was classified as a laboratory, field, WWTP, review or modelling study). Sixth, the country in which the study took place was noted. The bibliographic information and these

additional variables were used to analyse the database and produce the bibliographic analysis of literature on diclofenac, E2 and EE2. Further details on the systematic review methodology can be found in the Final Technical Report associated with this project.

Even following strict exclusion criteria, the final database that resulted from this systematic review includes 1268 relevant publications. Figure 2.1 demonstrates the very large number of articles returned by our searches and the number of articles excluded (and reasons for exclusion) during the title and abstract filters. The database of publications and the summary information regarding this database (bibliographic analysis) include all 1268 publications deemed eligible by the systematic review protocol. However, there were too many articles in the final database to complete a full text review of each of these publications. Consequently, the data used to answer the research questions proposed by this systematic literature review were compiled from recent review papers from the database of publications. In order to ensure all information was as recent and relevant as possible, only review papers from the database that were published from 2008 onwards were included; there were a total of 83 such review papers. All 83 of these publications were evaluated, and any summary data on three topics were extracted: (1) concentrations of diclofenac, E2 or EE2 in influent or effluent and their removal efficiencies during various wastewater treatments; (2) methods of detection and limits of detection (LODs) for each of the three compounds (Table 2.1); and (3) concentrations of these three PhACs in surface, ground or drinking water (Table 2.2). This information, which is summarised below and in the Final Technical Report, represents a review of recent reviews (Pautasso, 2013). This method ensures that our findings are unbiased and also presents the most current review of the sources, receptors and monitoring methods in Europe for diclofenac, E2 and EE2 to date.

2.1.3 Systematic review and bibliographic analysis results and conclusions

This section summarises the findings from the bibliographic analysis and answers the specific research questions concerning this systematic review. Control measures are not reviewed in this section because they are comprehensively covered in section 2.4 of this report.

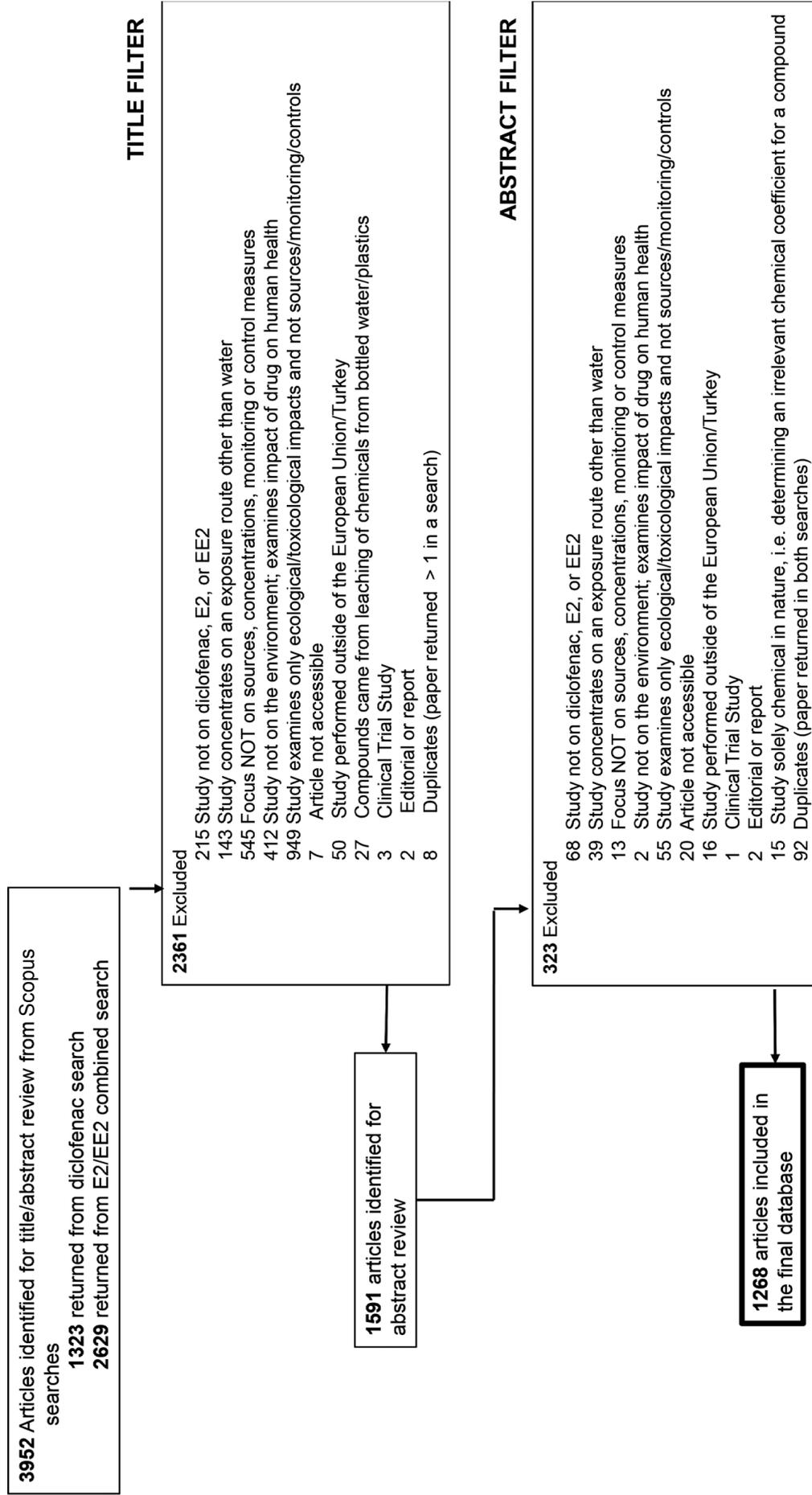


Figure 2.1. Publications (articles) returned from the systematic review searches. The figure shows the number of publications excluded with reasons for exclusion during the title and abstract filter, as well as the total number of publications included in the final database. Scopus is the largest abstract and citation database of peer-reviewed literature, including scientific journals, books and conference proceedings.

Table 2.1. Proposed WFD annual average environmental quality standard values for each of the three PhACs of interest compared to current detection limits reported in literature reviews. Data originate from review studies from the publication database (values in ng/L). If no method of detection is provided with a limit of detection value, values represent a summary (range or average) of a variety of different methods

Drug	Proposed AA EQS ^a	Current detection limits	Reference
Diclofenac	100 (EC, 2011)	LOD: 1 to 7	Vieno and Sillanpää (2014)
		LOD (for immunoassays): 6	Buchberger (2011)
		LOD (range in international studies): 0.25 to 100	Santos <i>et al.</i> (2010)
E2	0.4 (EC, 2011)	LOD: 0.008 to 40 ^b	Kunz <i>et al.</i> (2015)
		LOD: 0.6 to <26	Sosa-Ferrera <i>et al.</i> (2013)
		LOD (for measurements of steroids using LC-MS): 0.02 to 40	Tomšíková <i>et al.</i> (2012)
		LOD (for measurements of steroids using GC-MS): 0.01 to 500	
		LOD (range in international studies): 0.01 to 25	Santos <i>et al.</i> (2010)
		LOD (for measurements of oestrogens using GC-MS): 0.03 to <100	Briciu <i>et al.</i> (2009)
EE2	0.035 (EC, 2011)	LOD (for measurements of oestrogens using LC-MS): 0.003 to 200	
		LOD: 0.01 to 50 ^b	Kunz <i>et al.</i> (2015)
		LOD (for measurements of steroids using LC-MS): 0.02 to 40	Tomšíková <i>et al.</i> (2012)
		LOD (for measurements of steroids using GC-MS): 0.01 to 500	
		LOD (for immunoassays): 0.01 to 0.2	Buchberger (2011)
		LOD (range in international studies): 0.2 to 25	Santos <i>et al.</i> (2010)
		LOD (for measurements of oestrogens using GC-MS): 0.03 to <100	Briciu <i>et al.</i> (2009)
		LOD (for measurements of oestrogens using LC-MS): 0.003 to 200	
		LOD (for various analytical methods): 0.3 to 4.1	Clouzot <i>et al.</i> (2008)

GC-MS and LC-MS are analytical methods used to measure the concentration of compounds in samples.

LOD, limit of detection; MDL, method detection limit; GC-MS, gas chromatography–mass spectrometry; LC-MS, liquid chromatography–mass spectrometry.

^aAA EQS values are annual average environmental quality standards for inland surface waters, which, according to WFD legislation, encompass rivers and lakes and related artificial or heavily modified water bodies.

^bIndicates value was estimated from a figure.

The bibliographic analysis carried out by this study determined that the annual output of European research on diclofenac, E2 and EE2 has increased steadily from 1995 to 2015, with approximately 84% of all articles on aquatic contamination with these PhACs published since 2005 (Figure 2.2). In addition, Figure 2.2 shows that more studies are performed annually on the oestrogens than on diclofenac. This systematic review investigated three general themes regarding research on diclofenac, E2 and EE2: sources of contamination, receptors or monitoring methods used to measure the

levels of these compounds in aquatic environments, and control measures for reducing contamination. The bibliographic analysis found that studies focused on monitoring are more common than those on sources of contamination or control measures, although control measure studies have been on the rise in recent years. With regard to study type, laboratory-scale studies are the most common, while more realistic field and WWTP level studies are rarer (Figure 2.3). This can most likely be attributed to a lack of sensitive analytical techniques or accurate sensors. Finally, the bibliographic analysis

Table 2.2. Concentrations of each PhAC of interest in EU waters, including surface, ground and drinking water. Data originate from summary information provided in review studies from publication database; specific references listed for each PhAC. All values reported in ng/L. Values reported as minimum, maximum, range or mean, depending on what was reviewed by the reference

PhAC	Reference	Water type	Concentration
Diclofenac	Meffe and de Bustamante (2014)	Surface water	Maximum in Italian studies: 158
		Ground water	Maximum in Italian studies: n.d.
	Vieno and Sillanpää (2014)	Surface water	Generally below 100, almost always below 500
		Ground water	Generally low or below detection limits, maximum: 380
		Drinking water	Generally low or below detection limits: 1–7
	Rivera-Utrilla <i>et al.</i> (2013)	Surface water	Maximum of international studies between 1999 and 2004:1200
	Petrie <i>et al.</i> (2013)	Surface water	Range in UK: <0.5 to 261
		Surface water	Range in mainland Europe: <12 to 154
	Vazquez-Roig <i>et al.</i> (2013)	Surface water	Range in Spanish protected areas (wetlands, estuaries, watersheds): 1 to 90
	Jurado <i>et al.</i> (2012)	Ground water	Maximum in Spanish studies: 477
	Lapworth <i>et al.</i> (2012)	Ground water	International studies, maximum: 590; minimum: 2.5; mean: 121
	Ziylan and Ince (2011)	Surface water	Range of international studies: 1 to 1030
	Santos <i>et al.</i> (2010)	Surface water	Range in international studies: 0.3 to 147
		Ground water	Range in international studies: <10 to 50
		Drinking water	Range in international studies: <0.25 to <7
	Díaz-Cruz and Barceló (2008)	Surface water	Range in international studies: 15 to 135
	Zhang <i>et al.</i> (2008) ^a	Surface water	Range (mean) in international studies: <50 to 290
E2	Meffe and de Bustamante (2014)	Surface water	Maximum in Italian studies: 12.9
		Drinking water	Range in European studies: 0.20 to 2.1
	Kralchevska <i>et al.</i> (2013)	Surface water	European rivers: 0.11
		Drinking water	Range in European studies: 0.20 to 2.1
	González <i>et al.</i> (2012)	Surface waters	Studies in Llobregat river (Spain): n.d.
	Jurado <i>et al.</i> (2012)	Ground water	Maximum in Spanish studies: n.d.
	Lapworth <i>et al.</i> (2012)	Ground water	International studies, maximum: 120 ng/L; minimum: 0.79 ng/L; mean: 31 ng/L
		Surface water	Range of international studies, excluding outliers: 0.2 to 50
		Ground water	Range of international studies, excluding outliers: 0.08 to 2
	Pereira <i>et al.</i> (2011) ^a	Drinking water	Range of international studies, excluding outliers: n.d.
		Surface water	Range in international studies: <0.2 to 100
		Ground water	Range in international studies: 0.3 to 1.3
	Santos <i>et al.</i> , (2010)	Drinking water	In international studies: <0.50
		Surface water	Range in international studies: n.d to 200
		Ground water	Range in international studies: n.d. to 45
	Martin and Voulvoulis (2009)	Drinking water	Range in international studies: n.d. to 2
		Surface water	Range in international studies: 0.15 to 17
Drinking water		Range in international studies: 0.2 to 17	
EE2	Meffe and de Bustamante (2014)	Surface water	Maximum in Italian studies: 2.7
		Ground water	Maximum in Italian studies: n.d.
	Rivera-Utrilla <i>et al.</i> (2013)	Surface water	Maximum of international studies 1999–2004: 4.3
	Kralchevska <i>et al.</i> (2013)	Surface water	European rivers: 0.04
		Drinking water	Range in European studies: 0.15 to 2.4
	González <i>et al.</i> (2012)	Surface water	Studies in Llobregat river (Spain): n.d.
Jurado <i>et al.</i> (2012)	Ground water	Maximum in Spanish studies: n.d.	

Table 2.2. Continued

PhAC	Reference	Water type	Concentration
EE2	Pereira <i>et al.</i> (2011) ^a	Surface water	Range of international studies, excluding outliers: 0.5 to 50
		Ground water	Range of international studies, excluding outliers: 0.7 to 5
		Drinking water	Range of international studies, excluding outliers: 1 to 3
Santos <i>et al.</i> (2010)	Surface water	Range in international studies: <0.2 to 73	
	Ground water	Range in international studies: 0.5 to 3	
	Drinking water	In international studies: <0.1	
Martin and Voulvoulis (2009)	Surface water	Range in international studies: n.d to 831	
	Drinking water	Range in international studies: n.d. to 0.5	
Clouzot <i>et al.</i> (2008)	Surface water	Range in international studies: <0.2 to 5.1 (median range: 0.2 to 1.5)	
Wise <i>et al.</i> (2011)	Surface water	Range in international studies: <0.1 to 5.1	
	Drinking water	Range in international studies: 0.15 to 1.4	

^aIndicates value was estimated from a figure.

n.d., not detected.

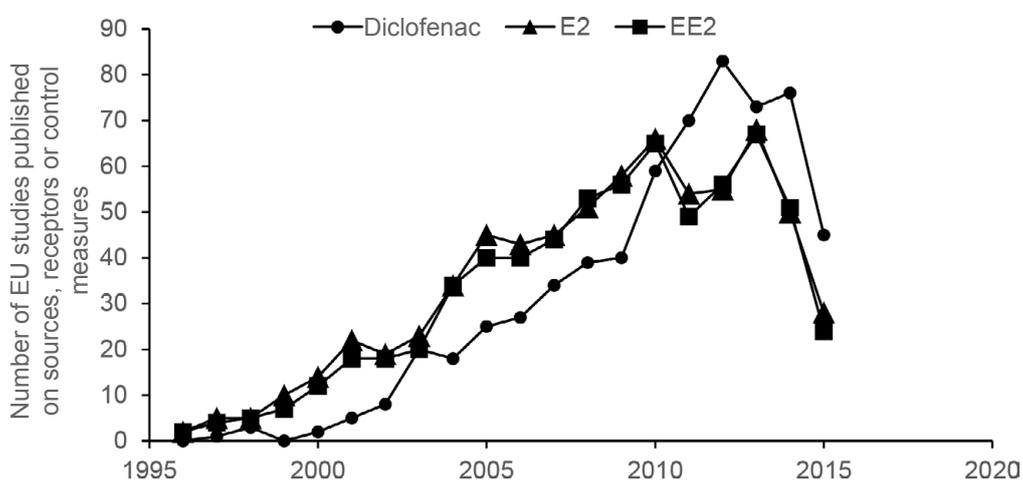


Figure 2.2. Total combined number of EU studies on sources, receptors, or control measures for diclofenac, E2 and EE2, from 1995 to May 2015.

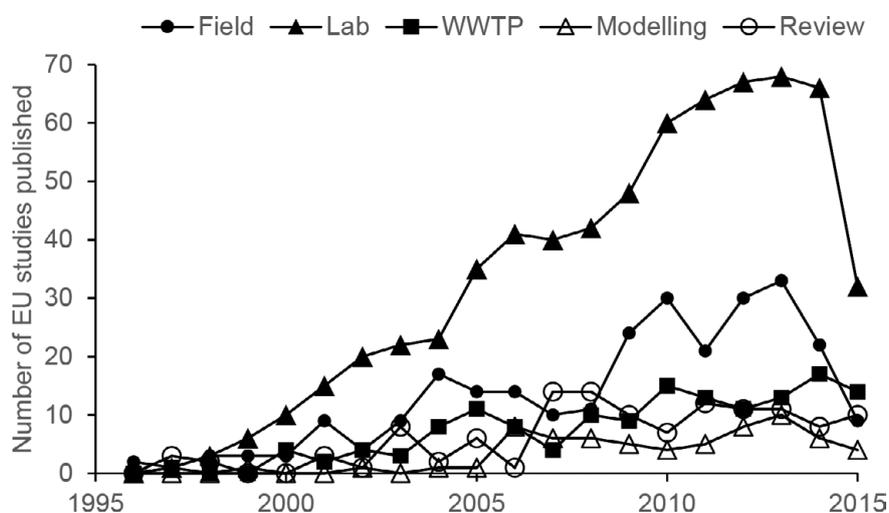


Figure 2.3. The number of studies on three PhACs (diclofenac, E2 and/or EE2) published in the EU from 1995 to May 2015 by type of study: field, laboratory scale, WWTP level, modelling and review.

determined that Spain and Germany are the European leaders in this field of research, while Ireland falls into the lower half of countries regarding research outputs.

Several of the review articles from the database of publications specifically aimed to summarise knowledge on the sources of environmental contamination of PhACs (including, and sometimes specifically addressing, diclofenac, E2 and EE2). According to these reviews, diclofenac and EE2 enter the European aquatic environment mainly as a result of human consumption and excretion of therapeutic drugs, followed by incomplete removal from influent at urban WWTPs (Burkhardt-Holm, 2010; Hecker and Hollert, 2011; Verlicchi *et al.*, 2012; Vieno and Sillanpää, 2014). E2 is a natural hormone excreted by humans which is also not completely removed during WWTP treatment, although livestock populations in Europe are also a significant non-point source of E2 contamination (Burkhardt-Holm, 2010; Hecker and Hollert, 2011; Wise *et al.*, 2011; Verlicchi *et al.*, 2012).

In order to address the second topic of this review, receptors and concentrations of the compounds of interest, Table 2.2 presents summary data on diclofenac, E2 and EE2 concentrations in EU surface, ground and drinking water. These data originate from the review studies that were analysed during this systematic review. Throughout Europe, diclofenac has on average higher concentrations (high ng/L or µg/L levels) in all aquatic matrices (including wastewater influent and effluent, and surface, ground and drinking water) than the hormones E2 and EE2 (ng/L range) (Miege *et al.*, 2008; Verlicchi *et al.*, 2012). However, this does not necessarily translate to higher negative environmental impact/risk to aquatic organisms (Burkhardt-Holm, 2010; Clouzot *et al.*, 2008). Diclofenac concentrations found in European surface waters are generally below the annual average (AA) EQS proposed by the WFD (100 ng/L) (EC, 2011), but several review studies report values exceeding this limit in the UK, Italy and other mainland European countries (Santos *et al.*, 2010; Ziylan and Ince, 2011; Ratola *et al.*, 2012; Petrie *et al.*, 2013; Rivera-Utrilla *et al.*, 2013; Meffe and de Bustamante, 2014; Vieno and Sillanpää, 2014). The data from the review studies suggest that typical surface water concentrations in Europe do not usually pose a significant environmental threat; however, point sources of pollution could lead to concerning levels of diclofenac contamination. E2 European surface water values are

usually less than 50 ng/L (Martin and Voulvoulis, 2009; Santos *et al.*, 2010; Pereira *et al.*, 2011; González *et al.*, 2012; Meffe and de Bustamante, 2014) but, nevertheless, such values greatly exceed the proposed AA EQS value (0.04 ng/L) of this bioactive compound (EC, 2011). Similarly, EE2 is either not detected or found at low levels in European surface waters (usually below 10 ng/L) (Clouzot *et al.*, 2008; Wise *et al.*, 2011; Rivera-Utrilla *et al.*, 2013; Meffe and de Bustamante, 2014), but reported values are often still higher than the proposed AA EQS value (0.035 ng/L) (EC, 2011). Compared with other steroid oestrogens, EE2 is detected in surface waters least frequently and at the lowest concentrations (Wise *et al.*, 2011); nevertheless, even trace amounts of this PhAC can cause endocrine disruption in aquatic organisms (Clouzot *et al.*, 2008).

Finally, current standard, laboratory-based, analytical chemistry methods are sufficiently sensitive for the detection and quantification of diclofenac (Vieno and Sillanpää, 2014). Limits of detection for E2 and EE2, however, are often higher than proposed AA EQS values (Santos *et al.*, 2010; Sosa-Ferrera *et al.*, 2013; Streck, 2009). Current detection limits reported by the review papers analysed during this systematic review are presented in Table 2.1; they confirm the existence of serious analytical challenges with regard to chemical monitoring methods and reporting for E2 and EE2.

2.2 Work Package 2: Mapping Irish Monitoring Data

2.2.1 Work package 2 aim

Whereas work package 1 focused on European research, the overall aim of the second work package was to identify and summarise all existing Irish research on diclofenac, E2 or EE2. If these three PhACs are added to future versions of the WFD priority substances list, an understanding of their levels in Irish waters will be critical. Therefore, this section of the project is particularly concerned with existing Irish monitoring data that can provide information on aquatic environmental concentrations of the three compounds of interest. In this work package, these monitoring data were reviewed, collated and mapped. This information was used to evaluate the mobility of these and other PhACs in an Irish context, and to identify potential pollution hotspots which may require additional future monitoring. This

work helps to identify national gaps in knowledge related to these three watch list PhACs.

2.2.2 Protocol for data collection and mapping of Irish monitoring data

Results from the literature review (section 2.1) indicated that research studies [many of them funded by the Environmental Protection Agency (EPA)] are the primary source of monitoring data for diclofenac, E2 and EE2. Therefore, in order to obtain all Irish monitoring data on these three PhACs, the database of publications that resulted from the systematic review (section 2.1) was utilised to search specifically for Irish studies. In addition, results from the systematic literature review that were rejected during the title or abstract filter were also reviewed, to ensure all Irish research was included. Relevant publications identified from the database were combined with sources from grey literature that was identified through the project team's personal network and through a series of semi-structured interviews (see Final Technical Report for more details). A total of 36 Irish studies which concerned at least one of the three compounds of interest were identified. These publications included five reports, three PhD theses and 28 peer-reviewed journal articles. A full text review was carried out for each of these publications and 21 were determined to contain relevant Irish monitoring data on diclofenac, E2 and/or EE2 in an aquatic matrix. Table A1 in the end of project report lists these publications and provides summary information about each one.

For each publication identified as containing relevant Irish monitoring data on diclofenac, E2 or EE2, several parameters were extracted for use in mapping. First, the date that water samples were taken was identified (including day, month and year if available, but year at minimum). The type of study (i.e. a study measuring the concentration of a compound or a study using effect-based methods), as well as the compound analysed [diclofenac, E2, EE2 or estradiol equivalent (EEQ)], was also identified. (EEQs are measured in effect-based methods.) The method of sampling (e.g. grab or passive) and the type of assay utilised was recorded, as was the matrix studied (marine water, lake water, ground water, effluent, etc.). The name of the specific location and the county where the sampling took place was noted. Global positioning system (GPS) co-ordinates for the sampling location were also identified, both in WGS84 and Irish National Grid. Co-ordinates of

sampling locations were either specified in the text of a publication or estimated based on descriptions of the sampling location. If the sampling location was a WWTP, its co-ordinates were recorded as the primary discharge point listed in the EPA wastewater licence (searchable online at <http://www.epa.ie/terminalfour/wwda/index.jsp?disclaimer=yes&Submit=Continue#VpPcJPmLTIX>). The concentration (in ng/L) of the compound recorded during each sampling event was also noted if it was available. If multiple samples were taken at the same location during a study (i.e. repeat sampling over time), each sampling event was listed separately. However, if multiple analyses were run on the same samples (i.e. tests run in duplicate or triplicate) the individual results were not reported; instead, the final value as presented by the authors of the study (usually an average) was utilised. In many cases, some of the required data were not available from the publications, in which case corresponding authors were contacted and a data request was made.

Two aspects of these data were mapped for this report, the distribution of the sampling events (or sampling effort) for each compound and the highest recorded concentrations of each compound at a sampling location. For the concentration data, effect-based studies were ignored and only concentration studies were considered. For some of these studies, concentration values were not available. This was because either the study reported only presence/absence of the compound or reported average values instead of raw data. In the latter case, authors were contacted in an attempt to obtain raw data values, though a small number of authors did not respond to data requests. These studies were, therefore, excluded from concentration mapping. The remaining concentration data were sorted by compound, location and value, and for each unique location the highest concentration recorded for each compound was identified for mapping. These concentration maps, therefore, represent the worst case scenario as recorded by monitoring studies to date at each location. This does not mean that these sites will always have such high concentrations of the compounds of interest; additional sampling events may have recorded lower values or non-detects (i.e. at a level below the reliable LOD). It should also be noted that just because a compound has not been detected at a site does not mean that it will not exceed WFD proposed limits; it is possible (especially for the oestrogens) that the LOD may exceed the WFD limit. Nevertheless, these maps

still provide an indication of which areas could be pollution “hotspots” based on currently available monitoring data. In addition to maps, the findings of all Irish studies on the PhACs of interest are summarised in the Final Technical Report for this project.

Data were mapped using ArcGIS Desktop software [Arc Catalogue and ArcMap 10.3.1, Environmental Systems Research Institute (ESRI)], using an ESRI single-user, 1-year licence to Athlone Institute of Technology). A file geodatabase was created to map the Irish sampling and concentration data on diclofenac, E2 and EE2. Sampling data compiled from previous research projects were read into ArcMap as .csv tables and exported as shapefiles in order to obtain full functionality. Shapefiles were then added to the file geodatabase as feature classes. Additional data used to create the file geodatabase were downloaded from the Central Statistics Office database “StatBank Ireland”, (<http://www.cso.ie/px/pxeirestat/statire/SelectTable/Omrade0.asp?Planguage=0>, utilised for county boundaries, city locations and population density) and the EPA’s Geo Portal (<http://gis.epa.ie/GetData/Download>, utilised for river basin catchments, WFD river basin districts, WWTP locations and attribute data, and WFD protected areas).

In order to provide a summary of national research on diclofenac, E2 and EE2, a review of the main Irish projects that have been carried out on each of these PhACs and the mapping results are presented in section 2.2.3.

2.2.3 Mapping Irish monitoring data results and conclusions

Main Irish projects on diclofenac, E2 and EE2

Five major national projects containing data relevant to this review were identified (Dempsey and Costello, 1998; Tarrant, 2005; Gill, 2009; Schmidt *et al.*, 2013; Giltrap *et al.*, 2013). In addition, an ongoing EPA-funded project investigating the use of passive sampling for monitoring emerging pollutants is also relevant; however, data from this work were not included in this report because the project is not yet complete. The results of our report, however, should be interpreted with consideration to this passive sampling project once its results become available.

Much of the current information about levels of diclofenac in the Irish aquatic environment comes from a project

funded by the EPA STRIVE programme (2007–2013) entitled “Pharmaceuticals in the Irish aquatic environment: the assessment and potential human impact of exposure to environmental contaminants on marine and freshwater bivalves” (Schmidt *et al.*, 2013). The overall aim of the project was to use a combination of chemical and biological analyses to assess the extent and effects of pharmaceutical pollution in the Irish aquatic environment; diclofenac was included as one of the pharmaceuticals of interest. This work produced two PhD theses and several peer-reviewed publications with data relevant to our project (Parolini *et al.*, 2011; Quinn *et al.*, 2011; Schmidt *et al.*, 2011; Schmidt, 2012; McEneff, 2013; McEneff *et al.*, 2013, 2014; Schmidt *et al.*, 2014). This is the only project that has produced significant data on the spatial occurrence and relative distribution of diclofenac in the Irish marine environment. It included study sites on both the east and west coasts of the country. This work includes measurements of diclofenac in effluent, surface water and biota.

Regarding the natural steroid oestrogen E2 and the synthetic oestrogen EE2, the most recent Irish monitoring was part of a 4-year EPA-funded project entitled “Biological effects and chemical measurements for the assessment of pollution in Irish marine waters (SeaChange)” (Giltrap *et al.*, 2013). A series of studies that were part of SeaChange quantified the levels of EDCs (including E2 and EE2) in the Irish marine environment, a task that previously had not been attempted. Of particular relevance to our study are data from a PhD project associated with SeaChange (Ronan, 2013), some of which were also published in a peer-reviewed article (Ronan and McHugh, 2013). During this work, a two-tiered spatial and temporal sampling approach was taken in order to study contaminants. Initially, nine Tier 1 locations were selected for measurement of EDCs in *Mytilus* spp. (using physiological biomarkers) and sediment ecotoxicology tests. Four of the Tier 1 locations were chosen for further Tier 2 sampling, which included comprehensive chemical and biological effects analysis of a variety of organisms and matrix types. Chemical analyses for E2 and EE2 were included in this Tier 2 sampling. Sampling locations for SeaChange were spread throughout the east, west and south coasts of Ireland, providing spatial data on these oestrogenic compounds. This project and the publications that resulted from SeaChange were critical in providing data on the spatial and temporal occurrence of E2 and EE2 in Irish marine waters and demonstrating that an

integrated approach is necessary to fully understand environmental contamination with these EDCs.

A second project funded by the EPA also monitored EDCs, but it investigated them as part of a larger study on septic tank and secondary treatment on-site wastewater systems (Gill *et al.*, 2005). This 3-year study aimed to use on-site field trials to better understand the performance of different subsoils in wastewater treatment of domestic effluent from septic tanks and small-scale secondary treatment applications. Two publications resulting from this project contained relevant E2 and EE2 monitoring data (Gill *et al.*, 2009; Ó Súilleabháin *et al.*, 2009). Given that the domestic wastewater of more than one-third of Ireland's population is treated by on-site systems (DELG, EPA and GSI, 1999), this study provides important information about a potentially significant national source of aquatic EDC contamination.

Two older reports were also published by the EPA on projects that investigated EDCs (including E2 and EE2) in the Irish aquatic environment. The first was a review of oestrogen-mimicking chemicals by Dempsey and Costello (1998) which mainly utilised data from international studies. This project focused on effect-based assessments and ultimately recommended that biological assessment be carried out in a variety of Irish waters, including municipal and industrial WWTP effluents and receiving waters. The second EPA-funded project on EDCs attempted to address this recommendation and culminated in a 2005 report by Tarrant *et al.* The objective of the Tarrant *et al.* (2005) project was to assess the risk from EDCs to Irish freshwater ecosystems and drinking water resources. The project consisted of three main studies. First, the authors conducted an *in vivo* caged fish study to determine the impacts of oestrogenic compounds from WWTP effluent from Ballincollig WWTP on exposed rainbow trout plasma vitellogenin levels in the River Lee, Co. Cork. No evidence of oestrogen exposure was found at any of the test or control sites in this experiment, indicating levels of oestrogens in the River Lee from this WWTP did not pose an environmental threat at that time (Tarrant *et al.*, 2005). Second, feral brown trout populations were surveyed for exposure to environmental oestrogens in the Rivers Liffey, Lee, and Bandon and the Killarney Lakes (Tarrant *et al.*, 2005). The results from this study were published in a 2008 paper (Tarrant *et al.*, 2008); the authors found

evidence of oestrogenic exposure only in fish from the River Liffey, downstream of Osberstown WWTP. The final study used the yeast oestrogen screen assay to determine the oestrogenic potency of the effluents from Irish WWTPs in the south and east of the country, as well as in some of their receiving waters (Tarrant *et al.*, 2005). Data from these studies are included in the maps created during this project.

Geographic information systems mapping of Irish data

From the publications listed in Table A1 in the end of project report, a total of 522 unique Irish monitoring data points were identified for diclofenac, E2, EE2 or EEQ concentration analysis. Of the samples, 151 were measurements of diclofenac concentrations, 83 each were measurements of E2 and EE2 concentrations and 205 were measurements of EEQ concentrations. These monitoring data included samples from 50 unique locations, comprised of influent or effluent from 16 Irish WWTPs, samples from 23 unique water bodies (including rivers, lakes, marine and transitional waters) and domestic effluent from seven locations.

Figure 2.4 demonstrates the distribution and frequency of the national monitoring data for diclofenac, E2, EE2 and EEQ concentrations over the entire period reviewed by this project, 1999–2014. It is clear from this figure that the oestrogens are better studied in an Irish context when compared with diclofenac; nine studies measured oestrogens or oestrogenicity in Irish surface or ground waters, but only two measured diclofenac. Overall, monitoring data for all three compounds are distributed relatively evenly throughout the country, though they are focused around population centres (Galway, Dublin and Cork). Given that high levels of pharmaceutical use in these cities could lead to the occurrence of pollution hotspots, it is important to continue to sample these locations. Much of the concentration data for all three compounds (indicated in Figure 2.4 by square, diamond and triangle symbols) is carried out in coastal water bodies (marine or transitional waters), rather than in inland surface waters (fresh waters). Concentration measurements of all three PhACs are particularly lacking in the midlands region. It is also clear from this figure that monitoring data on these compounds are lacking from the north, north-east and north-west coasts of Ireland.

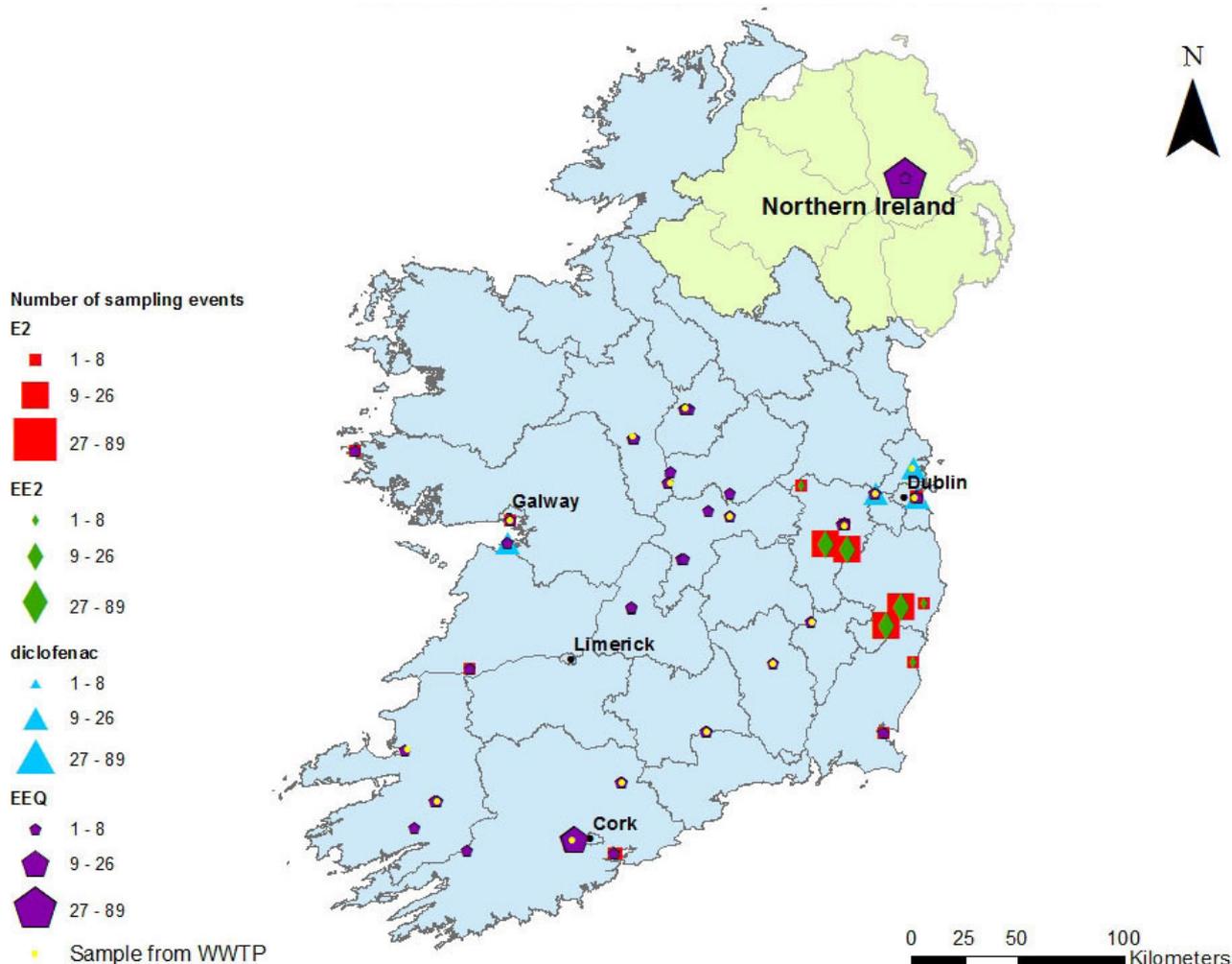


Figure 2.4. Summary of national monitoring distribution and frequency for diclofenac, E2, EE2 and estradiol equivalents in Ireland 1999–2014. Symbol size increases with increasing number of samples taken at each location.

Based on published data, out of approximately 1000 Irish WWTPs, 16 have been monitored for at least one of the three compounds of interest. This is similar to the monitoring rates of other European countries. Existing monitoring data from the five Irish WWTPs included in this study where diclofenac was measured indicate that this compound was found in treated effluents at levels which were at least as high as other European WWTPs and were sometimes higher (Lacey *et al.*, 2008; Lacey *et al.*, 2012; Loos *et al.*, 2012). However, this does not necessarily indicate a risk to human health because dilution/removal during treatment may reduce diclofenac concentrations below WFD proposed limits in surface and drinking waters. Measurements of E2 and EE2 in Irish WWTP effluents using chemical methods were rare; more often effluents were evaluated for total oestrogens (e.g. Tarrant *et al.*, 2005). The small

number of sampling events that attempted to measure specific E2 and EE2 concentrations did not detect either compound in two eastern Irish WWTPs (Jarošová *et al.*, 2014), but it is possible these compounds were present at levels below the LOD.

Figures 2.5–2.7 were created by mapping the highest concentration value recorded for each drug at each site where it was being monitored. These figures therefore allow for a comparison of the maximum recorded concentrations of each particular compound at the various sites for which monitoring data currently exist. It must be noted, however, that these sites may not always have concentrations of the compounds of interest as high as indicated by these figures. Additional sampling events may have recorded lower values or non-detects. Furthermore, it should also be noted that just because a

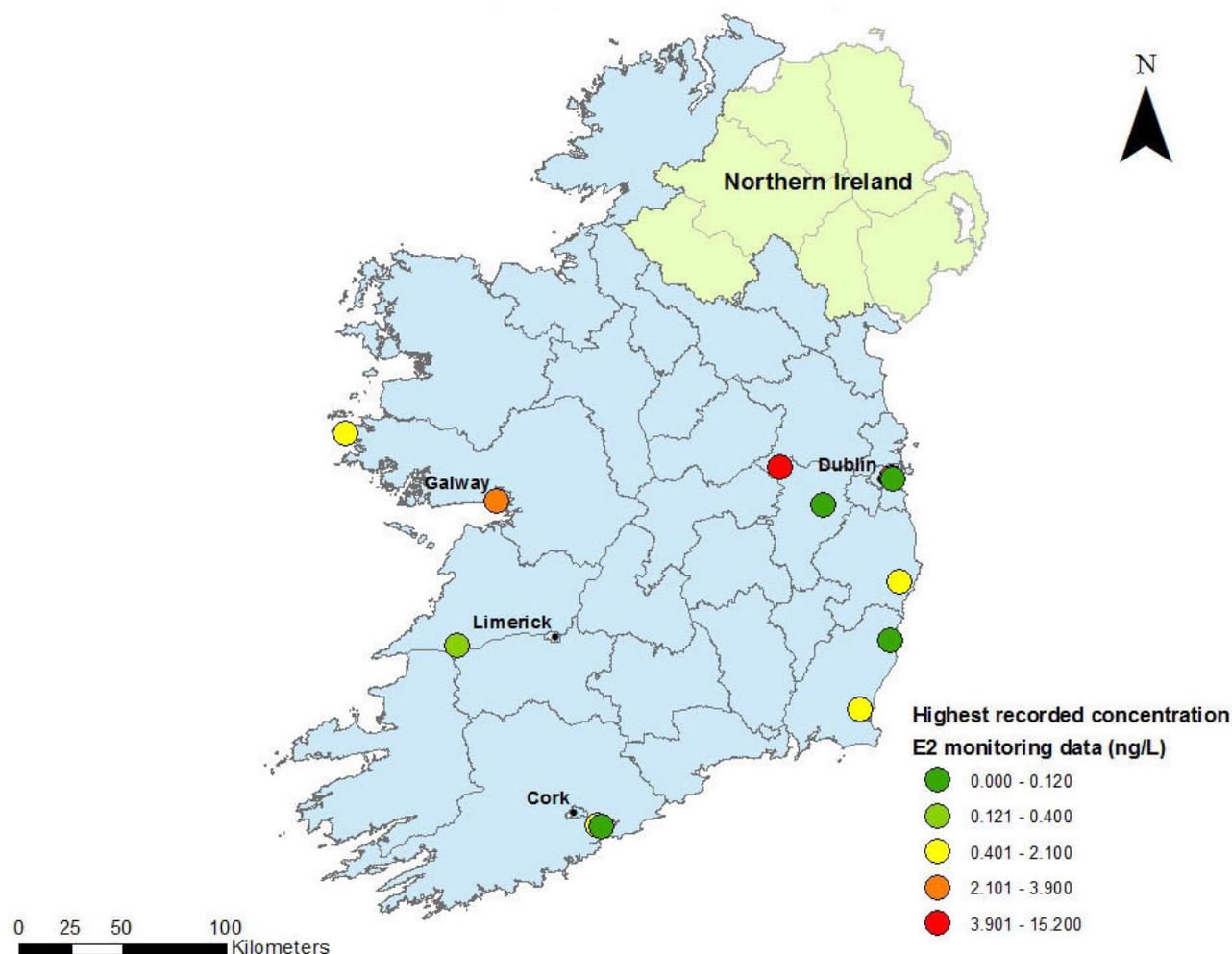


Figure 2.5. Highest recorded concentrations of E2 at sampling sites where concentration monitoring data were collected. Relative concentration values are indicated by the symbol colour, where low concentrations are indicated by greens and high by reds. Yellow, orange and red indicate sites where the highest recorded concentration was greater than the proposed WFD limit for E2 (0.4 ng/L).

compound has not been detected at a site (indicated by zero values in the figures) does not mean that it will not exceed WFD proposed limits; it is possible (especially for the oestrogens) that the LOD may exceed the WFD limit. Nevertheless, these maps provide an indication of which areas could be pollution “hotspots” based on currently available monitoring data.

Based on the limited Irish data extracted from the literature and mapped in this report, it would appear that the majority of Irish surface waters may not exceed WFD proposed AA EQSs for diclofenac (Figure 2.7) E2 (Figure 2.5) and EE2 (Figure 2.6), but that point sources of pollution could lead to occasional hotspots exceeding European limits. These hotspots would vary spatially and temporally, and may occur due to a variety of sources such as discharge points of high-risk WWTPs, high

densities of livestock near water sources, effluent from hospitals or pharmaceutical producers, and so forth. It should be noted that these predictions are based upon the use of very limited data and are especially uncertain for the oestrogens, because current LODs are too high to comply with reporting standards.

Drug utilisation data are available for diclofenac, E2 and EE2 in Ireland for 2008–2013 through the Health Service Executive through the Primary Care Reimbursement Services sector. These data would have been useful to this project because they could give an indication of the potential pollution hotspots based on areas where usage is high. Unfortunately, this short project was unable to obtain and format this complex dataset in time to include it extensively in maps.

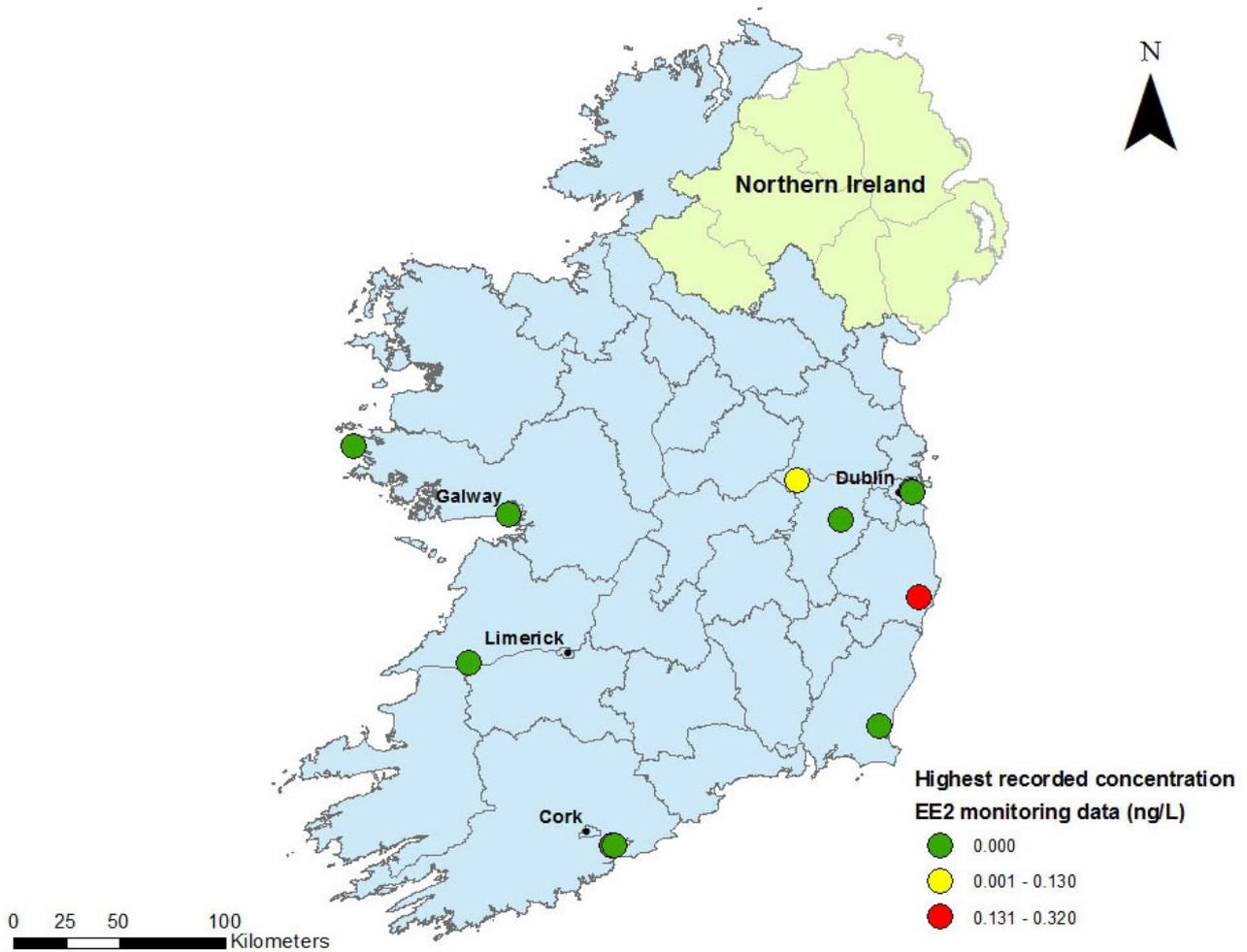


Figure 2.6. Highest recorded concentrations (ng/L) of EE2 sampling sites where concentration monitoring data were collected. Relative concentration values are indicated by the symbol colour, where low concentrations are indicated by greens and high by reds. Zero values represent no-detects.

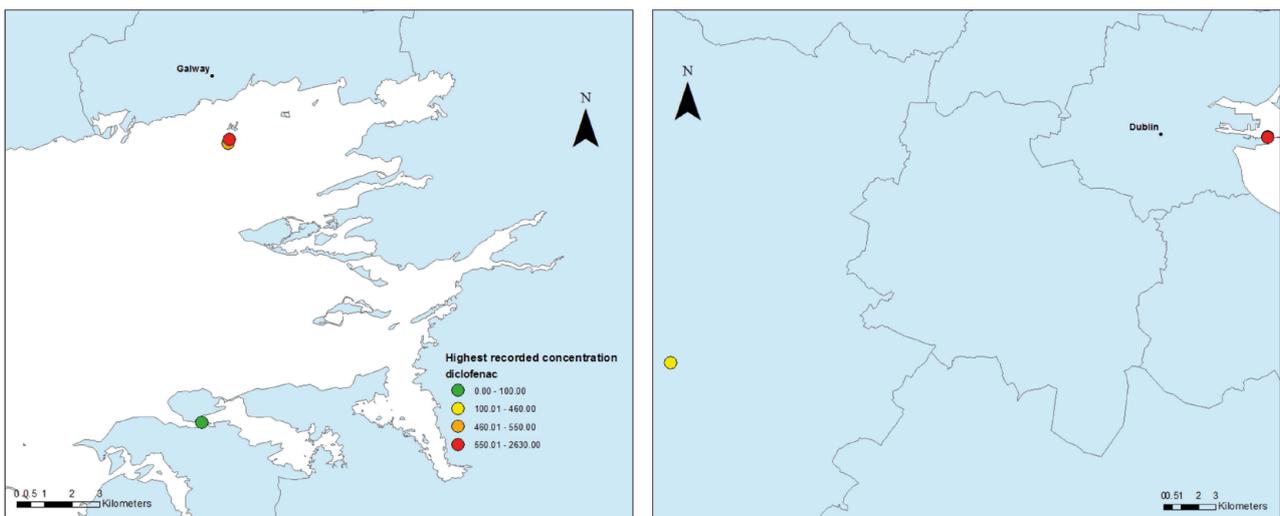


Figure 2.7. Highest recorded concentrations (ng/L) of diclofenac sampling sites where concentration monitoring data were collected. Relative concentration values are indicated by the symbol colour, where low concentrations are indicated by greens and high by reds. Yellow, orange and red indicate sites where the highest recorded concentration was greater than the proposed WFD limit for diclofenac (100 ng/L).

2.3 Work Package 3: Risk Assessment

2.3.1 Work package 3 aim

The primary aim of work package 3 was to develop a preliminary RA model for evaluating the environmental threat posed by Irish urban WWTPs with regard to pharmaceutical contamination of aquatic ecosystems. The purpose of this RA model is to identify urban WWTPs that are at high risk of negatively impacting the aquatic environment through contamination with the three WFD watch list pharmaceuticals of interest: diclofenac, E2 and EE2. This RA tool, especially if developed further, could potentially be used on a national scale to identify WWTPs that pose a particular risk related to these pharmaceutical pollutants, and to therefore prioritise the adoption of control measures. The model also identifies risk factors relevant to a variety of human pharmaceuticals, an emerging class of pollutants that is of ever-growing concern.

2.3.2 Protocol for risk assessment model development

Because of time constraints associated with this short project, the preliminary RA model we developed is semi-quantitative. The model was designed following the risk screening guidelines in section 10 (Drinking water safety plans) of the EPA's *Handbook on the Implementation of the Regulations for Water Service Authorities for Public Water Supplies* (EPA, 2010). Appendix 1 (Risk screening methodology for *Cryptosporidium*) was adapted to consider risk factors specific to the discharge of the PhACs of interest. The general principles of our model, therefore, align with this EPA-sanctioned risk-screening methodology. Similarly to the *Cryptosporidium* model, a scoring system was employed which enables determination of each WWTP

as low, medium or high risk (Table 2.3) for each PhAC of interest. For each of the three compounds, our model involves calculating a risk score for four main input parameters. These input parameters include catchment factors and treatment, operational and management factors (EPA, 2010), as well as compound-specific factors (Harris *et al.*, 2013).

The four main input parameters for our model are: (1) source of the influent coming into the WWTP (Table 2.4), (2) removal of compounds due to wastewater treatment (Table 2.5), (3) chemical properties of compounds (Table 2.6), and (4) fate of treated effluent (Table 2.7). A risk score is calculated for each input based on specific factors; the input risk scores are then added together, allowing for WWTPs to be ranked relative to each other (EPA, 2010). The factors used to calculate the risk score for each input variable are listed below in Tables 2.4–2.7. The use of these factors is justified and data sources for each are described in detail in this project's Final Technical Report.

This RA model was piloted by applying it to 16 Irish urban WWTPs that our systematic literature review and mapping work (work packages 1 and 2) identified as having existing monitoring data on diclofenac, E2, EE2 and/or EEQ. These included WWTPs of a range of sizes and treatment technologies, distributed relatively evenly throughout the country (see Table 2.8 for list, and the Final Technical Report for details on each WWTP used in the case study). The required data for each factor in all four inputs of our RA model was compiled for each of these 16 WWTPs. The cumulative risk score for each was then calculated and used to rank the WWTPs from highest to lowest risk of contamination of receiving waters with diclofenac, E2 and EE2. It must be noted that, because our model is not fully quantitative and because some key parameters could not be included due to time constraints, further

Table 2.3. Maximum possible risk score for each of the PhACs of interest for the novel RA model developed during this project and the relevant scoring system enabling each WWTP to be classified as high, medium or low risk. Scores are combined from four input parameters to determine the final risk category. This methodology allows the comparison of risks associated with each PhAC between WWTPs, but not between compounds at a given WWTP

	Diclofenac	E2	EE2
Highest possible score	32	40	33
High risk classification	≥21	≥27	≥24
Medium risk classification	10–20	14–26	12–23
Low risk classification	≤10	≤13	≤11

Table 2.4. Factors used in the RA model to calculate input 1 (source of influent) risk score. Light blue shading indicates parameters considered for all three compounds, light grey shading indicates parameters considered only for E2 and EE2, dark grey shading indicates parameters considered only for E2. The colour of the risk score indicates whether there is increased risk (positive values, red) or no impact on risk (zero values, blue)

Factor	Source factor description	Risk score	Actual score
1. WWTP-generated load	PE served: < 500	1	
	PE served: 501–5000	2	
	PE served: 5001–20,000	3	
	PE served: 20,001–50,000	4	
	PE served: > 50,001	5	
2. Domestic septic tank sludge/effluent received?	No	0	
	Yes	1	
3. Industrial sludge/effluent received?	No	0	
	Yes	1	
4. Gender ratio in county, women:men	≤ 1	0	
	> 1	1	
5. Cattle score	No cattle/calves in region	0	
	≤ 80 livestock unit per ha forage area in region	2	
	> 80 livestock unit per ha forage area in region	3	
6. Sheep score	No sheep or lambs in region	0	
	≤ 70 livestock unit per ha forage area in region	1	
	> 70 livestock unit per ha forage area in region	2	
7. Pig score	No pigs in county	0	
	≤ 20 livestock unit per ha forage area in region	1	
	> 20 livestock unit per ha forage area in region	2	
Total for input 1			

PE, population equivalent.

Table 2.5. Factors used in the RA model to calculate input 2 (removal during treatment) risk score. The colour of the risk score indicates whether there is increased risk (positive values, red), no impact on risk (zero values, blue) or decreased risk (negative values, green)

Factor	Treatment factor description	Risk score	Actual score
1. Tertiary treatment	Present year round	-4	
	Implemented seasonally	-2	
	Absent year round	0	
2. Type of secondary treatment (including nutrient removal)	Extended aeration (nitrogen removal)	-2	
	Sequence batch reactor (with or without phosphorus removal)	0	
	Conventional activated sludge (with or without phosphorus removal)	0	
3. WWTP quality measurement	Pass most recent UWWTD compliance criteria	0	
	Fail most recent UWWTD compliance criteria	1	
4. Monitoring data	Monitoring data demonstrate effluent levels below WFD limits or best-published PNEC values	-3	
	No monitoring data available	0	
	Monitoring data demonstrate effluent levels above WFD limits or best-published PNEC values	3	
Total for input 2			

UWWTD, Urban Wastewater Treatment Directive; PNEC, Predicted no-effect concentration.

Table 2.6. Factors used in the RA model to calculate input 3 (chemical properties of compounds) risk score. The colour of the risk score indicates whether there is increased risk (positive values, red) or no impact on risk (zero values, blue)

Factor	Chemical properties factor description	Risk score	Actual score
1. Metabolism	Rate of excretion 0–25%	1	
	Rate of excretion 26–50%	2	
	Rate of excretion 51–75%	3	
	Rate of excretion 76–100%	4	
2. Sorption potential	Low water solubility/high hydrophobicity, identified through K_{ow} , D_{ow} , and K_d values, and reports from literature	1	
	High water solubility/low hydrophobicity, identified through K_{ow} , D_{ow} , and K_d values, and reports from literature	4	
3. Degradation potential	High levels of degradation through photolysis, hydrolysis or other mechanisms, identified through compound half-life in the environment and reports from literature	1	
	Low levels of degradation through photolysis, hydrolysis or other mechanisms, identified through compound half-life in the environment and reports from literature	3	
4. Potential for deconjugation of conjugated metabolites during treatment	Not found to occur in the literature	0	
	Low potential, identified through literature	1	
	High potential, identified through literature	2	
Total for input 3			

Table 2.7. Factors used in the RA model to calculate input 4 (fate of treated effluent) risk score. The colour of the risk score indicates whether there is increased risk (positive values, red) or no impact on risk (zero values, blue)

Factor	Fate factor description	Risk score	Actual score
1. Type of receiving water	Coastal	1	
	Transitional/estuary/river/lake	2	
	Stream	3	
	Ground	4	
2. Proximity to sensitive area	Primary discharge location not at/near sensitive area	0	
	Primary discharge location at/near sensitive area	1	
3. Flow of receiving water	High	1	
	Medium	2	
	Low	3	
Total for input 4			

model development should be undertaken before it is implemented on a national scale or used for regulatory purposes. In addition, this model is designed to compare the environmental risk between WWTPs with regard to emission of each of the three PhACs of interest. Because the factors considered for certain inputs vary between compounds, this model should not be used to compare risks directly between compounds at the same WWTPs.

2.3.3 Risk assessment results and conclusions

In order to test this preliminary RA model and evaluate its effectiveness for identifying WWTPs at high risk with respect to the environmental consequences of diclofenac, E2 or EE2 pollution, we carried out a case study using 16 Irish WWTPs. Results from this case study are presented in Table 2.8.

Table 2.8. Results of case study evaluating 16 Irish WWTPs using the developed RA model for diclofenac, E2 and EE2. WWTPs are ranked for each PhAC from highest to lowest risk, based on the cumulative (total) risk scores assigned by the model. The different colours indicate different cumulative risk scores, red (higher risk) to green (lower risk), and WWTPs that share the same colour had the same final score and are ranked equally. Grey indicates the lowest level of risk after black. “Risk classification” indicates the classification of the cumulative risk score by the model

Diclofenac		E2		EE2	
WWTP name	Risk classification	WWTP name	Risk classification	WWTP name	Risk classification
Leixlip	High	Leixlip	Medium	Leixlip	Medium
Osberstown	High	Kilkenny	Medium	Kilkenny	Medium
Kilkenny	High	Osberstown	Medium	Osberstown	Medium
Killarney	High	Killarney	Medium	Killarney	Medium
Longford	High	Longford	Medium	Longford	Medium
Ringsend	High	Fermoy	Medium	Fermoy	Medium
Galway	High	Tullamore	Medium	Tullamore	Medium
Fermoy	High	Carlow	Medium	Roscommon	Medium
Tullamore	High	Clonmel	Medium	Carlow	Medium
Roscommon	Medium	Ringsend	Medium	Clonmel	Medium
Swords	Medium	Roscommon	Medium	Ringsend	Medium
Carlow	Medium	Athlone	Medium	Athlone	Medium
Clonmel	Medium	Ballincollig	Medium	Ballincollig	Medium
Athlone	Medium	Tralee	Medium	Tralee	Medium
Ballincollig	Medium	Galway	Medium	Galway	Medium
Tralee	Medium	Swords	Medium	Swords	Medium

Table 2.8 demonstrates that five out of the sixteen WWTPs included in the RA case study were identified as posing the greatest aquatic environmental risk with regard to diclofenac, E2 and EE2: Leixlip, Osberstown, Kilkenny, Killarney and Longford. Interestingly, these five plants vary in terms of their spatial distribution: Leixlip and Osberstown are eastern WWTPs, Kilkenny is located in the south-east, Longford is in the midlands and Killarney is in the west. Common characteristics of these plants that contributed to their high-risk rating included large WWTP-generated load; no tertiary treatment and a lack of extended aeration; existence of monitoring data indicating high levels of the relevant PhACs in treated effluent; primary discharge point near/at a sensitive area; and discharge into receiving waters with low 95 percentile flow rates. At the other end of the risk scale, two WWTPs included in the case study were identified as the lowest risk with regard to the three PhACs of interest: Ballincollig and Tralee. These two WWTPs received lower overall scores because the process configuration of these plants is expected to increase removal efficiencies. Generally, the results from this case study are in agreement with the limited

existing diclofenac, E2 and EE2 monitoring data available from these Irish WWTPs.

Figure 2.8 demonstrates the distributions of the cumulative risk scores of the 16 WWTPs from the diclofenac, E2 and EE2 models. The high scores associated with diclofenac can largely be attributed to the high input 3 score this recalcitrant compound received. E2 scores were similarly high because of the additional factors included in the model in input 1 (livestock densities). EE2 scores were lower because the input 3 score was low due to the high potential of oestrogens for biodegradation and sorption, and because only four factors were included in input 1 for this model. These considerations further demonstrate why direct comparisons of the risk scores between compounds at individual WWTPs cannot be made using the current RA models. Even though the risk classifications assigned to WWTPs in this study were always high or medium, the overall distribution of risk scores was sufficient to allow for a meaningful risk ranking of these WWTPs (Table 2.8 and Figure 2.8). One reason that no WWTPs were classified as low risk was the size of the WWTPs: the smallest

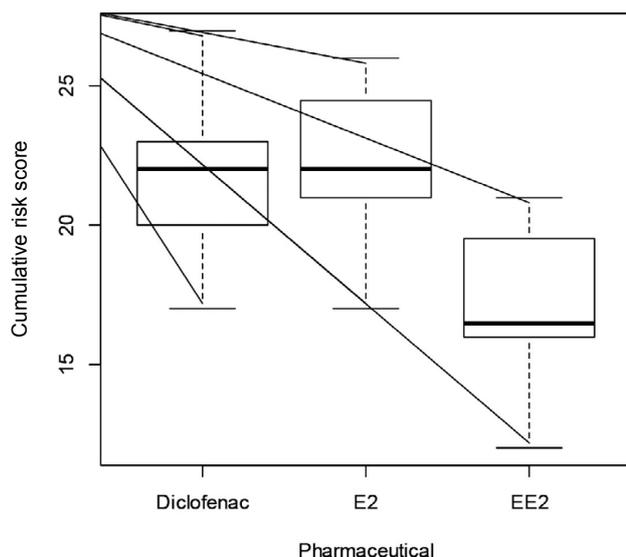


Figure 2.8. Comparison of the distribution of cumulative (total) risk scores assigned during the case study to the 16 WWTPs included for analysis by the RA model for diclofenac, E2 and EE2.

plant had a PE (population equivalent) of 6989, therefore all plants received a high risk score for this factor. In addition, several of the plants classed as medium risk could achieve low risk status if they employed process configurations known to reduce levels of pharmaceuticals. Obtaining higher quality data would increase the range of the final cumulative risk scores and could lead to some WWTPs being classified as low risk (see Final Technical Report for further suggestions for model improvement).

Input 3 of this RA model (Table 2.6) is the only input specific to the PhACs of interest, i.e. the risk score for this input depends only on the physiochemical properties and behaviour of the compound of interest. The total input 3 scores for diclofenac, E2 and EE2 are twelve, five and six, respectively. According to our model, of these three compounds, diclofenac presents approximately twice the risk of being found in receiving waters compared with E2 or EE2. This finding is consistent with reports from the literature that diclofenac is among the most recalcitrant pharmaceuticals (Patrolecco *et al.*, 2015), and that its removal percentages during wastewater treatment, though variable, are on average much lower than those of E2 or EE2 (Luo *et al.*, 2014; Vieno and Sillanpää, 2014). In addition, the input 3 scores for E2 and EE2 indicate that the latter is slightly more persistent after wastewater treatment. This is also consistent with findings reported in the literature, which

show that EE2 is considerably more recalcitrant than E2 and its removal rates in activated sludge treatment plants (the conventional approach to wastewater treatment) are more variable (Petrie *et al.*, 2014).

Future RA work regarding PhACs in the aquatic environment should ensure that this model aligns with approaches already utilised by national regulatory bodies such as the EPA. For example, the EPA has adopted the World Health Organization's (WHO) Water Safety Plan approach in relation to public drinking water supplies (EPA, 2011). This approach calls for the identification of all potential risks to the water supply, from catchment to consumer, in order to put in place appropriate mitigation measures. It would benefit this model, as well as update the 2009 WHO-based approach, if the two were considered together and complemented each other.

Although preliminary, this case study demonstrates the usefulness of this basic, semi-quantitative RA model for determining the relative risks posed by Irish WWTPs with regard to environmental consequences of contamination with the PhACs of interest. Future extensions and developments of this RA model could allow benchmarking with EU standards, as well as development for applicability with a wide range of established and emerging aquatic pollutants, thus providing critical information to regulators, service providers and decision makers.

2.4 Work Package 4: Control Measures

2.4.1 Work package 4 aim

In order to mitigate against pollution of the aquatic environment with these watch list PhACs, control measures that can reduce or eliminate the risks posed by these compounds must be evaluated. A critical understanding of control measures in an Irish context will be important if these compounds are added to future WFD priority substances lists. As a result, the last work package for this project aimed to review the efficacy of existing and emerging international control measures (and in particular treatment options) for diclofenac, E2 and EE2. This summary of control measures focuses on the main source of pollution for most PhACs: incomplete removal during wastewater treatment. The information summarised in this section is also compiled into a toolkit, comprising easily digestible tables, to aid relevant

stakeholders that are considering the implementation of these measures at Irish WWTPs.

2.4.2 Protocol for control measures data collection

This evaluation of control measures was completed through a review of the literature. In order to source information for this section, the database of publications from the systematic literature review from work package 1 was searched (section 2.1). A large body of research has been conducted to date regarding control measures for diclofenac, E2 and EE2. Because of this vast amount of literature, it was impossible to consider all relevant publications from the database. Instead, key word searches were used in the database to obtain relevant publications for each section of the control measures review. Additional articles and sources from the grey literature (e.g. government reports) were also utilised. These sources were found from additional database searches and government websites (e.g. www.epa.ie; www.epa.gov). The resulting review is, therefore, not a systematic or complete evaluation of every control measure employed to treat diclofenac, E2 and EE2; it is instead a review of the most relevant information.

The information reviewed in this section of the report is broken down into three main topics. First, the physiochemical properties of diclofenac, E2 and EE2 and the resulting impacts on removal of these compounds during wastewater treatment are reviewed. Second, the effectiveness of conventional wastewater treatment (specifically activated sludge) for the removal of each of these compounds is discussed. Finally, what is known about the capacity of existing and emerging tertiary (or advanced) treatments for removing diclofenac, E2 and EE2 from treated wastewater is summarised. Detailed text summarising the research on these three main topics can be found in the Final Technical Report associated with this project. This information has also been distilled into easily digestible tables (see section 2.4.3). These tables are meant to serve as a toolkit that will help inform wastewater treatment practitioners and other users how best to control for these three watch list PhACs at WWTPs (note: the summary table on the physiochemical properties of diclofenac, E2 and EE2 has been omitted here but is provided in the Final Technical Report). A brief summary of the findings from this work package is also provided.

2.4.3 Control measures results and conclusions

Physiochemical properties impacting PhAC removal from wastewater

The findings from this work package revealed that the two pathways that are most important for the removal of organic compounds (i.e. PhACs) during wastewater treatment are sorption to organic matter and biotransformation/biodegradation (Clara *et al.*, 2005b; Drewes, 2007). Overall, PhACs with high water solubility (i.e. with a low potential for sorption) and low biodegradability are the most recalcitrant during wastewater treatment. Certain physiochemical properties or experimentally determined constants can be used to predict the extent of removal of PhACs during wastewater treatment through these two removal pathways. The most commonly used examples in the literature include the octanol–water partition coefficient (K_{ow}), n-octanol–water partition coefficient (D_{ow}), solid–water distribution coefficient (K_d), half-life and the biodegradation constant (K_{bio}). Definitions and descriptions of each of these parameters, as well as values specific to diclofenac, E2 and EE2, can be found in the Final Technical Report associated with this project. Diclofenac is fairly soluble in water because of its physiochemical properties; this compound ionises at neutral pH, and becomes electronically neutral at acidic pH. These physiochemical properties are directly related to diclofenac's behaviour during wastewater treatment (reviewed in Vieno and Sillanpää, 2014). E2 and EE2, in contrast, are only weakly soluble in water and their physiochemical properties indicate that they will be more likely to be removed during wastewater treatment by sorption onto organic matter and/or biodegradation (Martín *et al.*, 2012; Ben Fredj *et al.*, 2015).

PhAC removal during conventional wastewater treatment

This work package next addressed the removal of each of the PhACs of interest by conventional wastewater treatment technologies. A review of the generalities of municipal wastewater treatment found that, typically, pre-treatment and primary treatment steps are used to remove solids and inorganic matter, followed by secondary treatments to remove organic matter. Secondary conventional wastewater treatment based on activated sludge is most commonly used to treat large volumes

of wastewater (Martín *et al.*, 2012). Conventional activated sludge (CAS) is an aerobic suspended growth treatment process utilising an aeration basin in which air or oxygen is forced into a sewage liquor developing a biological floc capable of reducing the content of organic matter (Camacho-Muñoz *et al.*, 2012). A further description of some of the process parameters and configurations of CAS treatment that can impact PhAC removal is provided in the Final Technical Report associated with this project.

A summary of the effectiveness of CAS treatment for removal of diclofenac, E2 and EE2 is provided in the toolkit in Table 2.9. Studies show that diclofenac is poorly removed during CAS treatment; removal percentages are variable but generally fall between 21 to 40% (Luo *et al.*, 2014), although negative removal rates have also been reported in Irish WWTPs (Lacey *et al.*, 2008; Lacey *et al.*, 2012). Mean diclofenac concentrations in European municipal influents are between 0.11 and 2.3 µg/L (110 and 2300 ng/L) and effluents are

between 0.002 and 2.5 µg/L (2 and 2500 ng/L) (Vieno and Sillanpää, 2014). In contrast, E2 and EE2 are generally highly removed during conventional wastewater treatment and removal percentages generally are 85% or greater for these two compounds (Luo *et al.*, 2014). Irish data on removal of E2 and EE2 following wastewater treatment do not exist, because these compounds were not detected in influents or effluents (Jarošová *et al.*, 2014). Final European effluents normally contain nanogram per litre concentrations of these compounds (Griffith *et al.*, 2014), but EE2 is consistently more recalcitrant than E2 (Petrie *et al.*, 2014) to conventional wastewater treatment.

Removal of PhACs using advanced treatments

Primary and secondary treatments are not specifically designed to remove trace concentrations of complex organic pollutants, such as PhACs (EPA, 1997; Fatta-Kassinos *et al.*, 2011; Verlicchi *et al.*, 2012). As a result,

Table 2.9. Impact of conventional activated sludge on removal of PhACs of interest during wastewater treatment

PhAC	Sorption to sludge	Degradation potential	HRT	SRT	Removal efficiency (conventional activated sludge)
Diclofenac	Low potential; sorption to sludge observed to a low degree (Ternes <i>et al.</i> , 2004; Radjenović <i>et al.</i> , 2009; Martín <i>et al.</i> , 2012; Suárez <i>et al.</i> , 2012; Patrolecco <i>et al.</i> , 2015)	Low potential; poorly biodegradable (Joss <i>et al.</i> , 2005; Quintana <i>et al.</i> , 2005; Joss <i>et al.</i> , 2006)	Elimination of diclofenac could be enhanced by increasing HRT to more than 2–3 days; would increase the contact time of water with the biomass (Suárez <i>et al.</i> , 2012)	Enriching the bioreactor with diclofenac-degrading microbes may enhance elimination; could be achieved by applying a SRT > 150 days (Fernandez-Fontaina <i>et al.</i> , 2012)	Variable but generally poorly removed; 0–81.4% (Luo <i>et al.</i> , 2014); mean concentrations in European municipal influents between 0.11 and 2.3 µg/L (110 and 2300 ng/L), effluents between 0.002 and 2.5 µg/L (2 and 2500 ng/L) (Vieno and Sillanpää, 2014)
E2 and EE2	Moderate potential; susceptible to removal by sorption (Ternes, 2006; Carballa <i>et al.</i> , 2008; Zhang and Zhou, 2008; Martín <i>et al.</i> , 2012; Ben Fredj <i>et al.</i> , 2015)	High potential; generally biodegraded very effectively in WWTP processes under aerobic and anaerobic conditions (Abargues Llamas <i>et al.</i> , 2012; Alvarino <i>et al.</i> , 2014; Petrie <i>et al.</i> , 2014)	Biodegradation was increased when the HRT was optimised by extending it from 8 to 24 hours (Petrie <i>et al.</i> , 2014)	Maximum achievable removal when at the maximum SRT studied (27 days) (Petrie <i>et al.</i> , 2014); critical SRT of 10 days for removal of natural oestrogens and some micropollutants suggested (Clara <i>et al.</i> , 2005a)	Highly removed: E2, 92.6–100% (Luo <i>et al.</i> , 2014); EE2, 43.8–100% (Luo <i>et al.</i> , 2014); reduced by ~85%. Final effluents normally contain nanogram per litre concentrations (Griffith <i>et al.</i> , 2014) EE2 typically more recalcitrant than E2 (Petrie <i>et al.</i> , 2014)

Increased HRT increases the contact time of water with the biomass, potentially leading to higher removal rates of PhACs; increased SRT leads to increased microbial diversity, which can increase the metabolising and transforming capabilities of the sludge, therefore increasing PhAC removal.

HRT, hydraulic residence time; SRT, solids retention time.

tertiary (also known as advanced) treatments are often utilised to remove persistent organic pollutants, including many PhACs, from treated wastewater (Suárez *et al.*, 2008; Kümmerer, 2009; Oulton *et al.*, 2010; Rivera-Utrilla *et al.*, 2013). In particular, recent studies have investigated four types of tertiary treatment technologies for removal of PhACs from treated wastewater, including oxidation technologies, membrane filtration, the use of activated carbon (AC) and constructed wetlands (CW) [(Kümmerer, 2009; Kümmerer, 2010) see Table 2.10]. Details of each of these treatments, including a more extensive description as well as general advantages and disadvantages, are available in the Final Technical Report.

The effectiveness of each of the four main types of advanced treatment technologies listed above for removal of diclofenac, E2 and EE2 from treated wastewater is presented in the toolkit, in Table 2.11. Overall, research indicates that oxidation technologies are considered highly efficient at diclofenac removal, often achieving >90% removal of this compound (Ziylan and Ince, 2011; Ribeiro *et al.*, 2015). Membrane filtration can also be efficient at removing diclofenac from treated wastewater, but it depends on the technology used; micro and ultra filtration are typically ineffective, while nano and reverse osmosis filtration are very efficient for removal of this particular PhAC (Kimura *et al.*, 2003; Snyder *et al.*, 2007; Suárez *et al.*, 2008). The application of AC can effectively reduce diclofenac concentrations in treated wastewater, but removal rates largely depend on operational variables (Delgado *et al.*, 2012). Finally, CWs demonstrate variable removal

of diclofenac, but this compound is considered recalcitrant in these systems (Matamoros and Bayona, 2008; Oulton *et al.*, 2010).

For E2 and EE2 removal, oxidation technologies are considered very effective treatments and can reportedly remove 94–99% of these compounds (Pereira *et al.*, 2011). Membrane filtration technologies, while exhibiting more variation than oxidation technologies, can also be extremely effective at oestrogen removal (Koh *et al.*, 2008; Braeken and Van der Bruggen, 2009; Dudziak and Bodzek, 2009). The use of AC is also appropriate for oestrogen removal, but, similar to diclofenac removal, rates depend on operational variables and wastewater characteristics (Koh *et al.*, 2008; Delgado *et al.*, 2012). Finally, CWs can perform oestrogen removal, but the effectiveness depends upon the configuration and design of the system (Matamoros and Bayona, 2008).

Although more information is needed to accurately model the benefits of using tertiary treatments to reduce PhAC concentrations in treated wastewaters, in general the literature suggests that the environmental benefits may not outweigh the costs (Corominas *et al.*, 2013). Some sources suggest that it may currently be more economically advantageous to adapt conventional wastewater treatment operational variables to decrease PhAC emissions, rather than to incur the costs/complications of adding tertiary treatments (Jones *et al.*, 2007). However, there is a large amount of uncertainty regarding the environmental impacts of aquatic contamination with PhACs; this issue needs to be addressed to strengthen cost–benefit analyses of advanced treatments.

Table 2.10. Descriptions, advantages and disadvantages of the main advanced (tertiary) treatment technologies investigated during this work package

	Membrane filtration	Activated carbon	Oxidation technologies	Constructed wetlands
Description	Membranes or media of various sizes and types utilised to filter wastewater (Oulton <i>et al.</i> , 2010)	Activated carbon provides high surface area for PhACs to sorb to; applied in granular or powdered form (Delgado <i>et al.</i> , 2012)	Application of chemical or physical oxidation processes for the treatment of organic pollutants (Ribeiro <i>et al.</i> , 2015)	Land-based systems comprised of shallow ponds/beds; utilise natural attenuation processes to treat wastewater (Oulton <i>et al.</i> , 2010)
Main advantages	Lack of toxic by-products, disinfection	Lack of toxic by-products	Lack of harmful residuals after treatment, short contact time, disinfection	Less energy input; minimal expertise required to run these systems
Main disadvantages	Membrane fouling	Waste generation/sorbent replacement	Formation of toxic by-products	Requires large surface area, long retention times

Table 2.11. Impact of various tertiary treatment types on removal of PhACs of interest during wastewater treatment

Technology	Diclofenac removal	E2/EE2 removal	Costs	Bi-product danger
Membrane filtration technologies	Highly dependent on filtration technology; poor for micro and ultra filtration, can be efficient for nano and reverse osmosis (Kimura <i>et al.</i> , 2003; Snyder <i>et al.</i> , 2007; Suárez <i>et al.</i> , 2008)	Variable depending on technology; removal by nanofiltration ranges from > 50%–90 % (Koh <i>et al.</i> , 2008; Braeken and Van der Bruggen, 2009; Dudziak and Bodzek, 2009)	Capital costs include construction, engineering, materials costs, operational and management costs include replacing membranes and power to pump wastewater (USEPA, 1999a)	None (USEPA, 1999a)
Activated carbon	Can be efficient, depending on operational variables (Delgado <i>et al.</i> , 2012)	Can be efficient, depending on operational parameters and wastewater characteristics (Koh <i>et al.</i> , 2008; Delgado <i>et al.</i> , 2012)	Dependent on different carbon contactor configurations and the cost of on-site vs off-site regeneration, as well as site and wastewater characteristics; capital costs include carbon contactors, storage tanks, regeneration systems, etc. and operational costs include purchase of carbon, electrical power, flushing of carbon slurry piping, etc. (USEPA, 2000b)	None (Rivera-Utrilla <i>et al.</i> , 2013)
Oxidation technologies	Highly efficient processes for diclofenac removal (>90%) (Ziylan and Ince, 2011; Ribeiro <i>et al.</i> , 2015)	Highly efficient process for oestrogen removal (94–99%) (Pereira <i>et al.</i> , 2011)	Dependent on technology type, capacity of the plant, wastewater characteristics, manufacturer and the site; e.g. ozonation costs generally high compared with other technologies, while UV can be competitive (USEPA, 1999b,c)	High for diclofenac (Sein <i>et al.</i> , 2008) and oestrogenic compounds (Pereira <i>et al.</i> , 2011)
Constructed wetlands	Very variable removal rates, diclofenac considered recalcitrant compound (Matamoros and Bayona, 2008; Oulton <i>et al.</i> , 2010)	Variable removal rates but can be effective (>90%) depending on configuration and design parameters (Matamoros and Bayona, 2008)	Major capital costs include purchasing land, liner costs, engineering, etc. but both capital and operational and management costs tend to be much lower than conventional wastewater treatments (USEPA, 2000a,c)	

3 Conclusions and Future Research Needs

The overall aim of this project was to provide a baseline study for Ireland, exploring the implications of the addition of diclofenac, E2 and EE2 to the WFD priority substances list. This project utilised a systematic literature review to summarise the European state of knowledge with regard to the sources and prevalence of these PhACs. It mapped all national concentration data and reviewed Irish-specific research. The environmental risk posed by Irish WWTPs with regard to PhAC contamination was also assessed in order to align the country with European standards and research in this field. Finally, a critical analysis of the effectiveness of potential control measures was carried out.

3.1 Main Project Conclusions

Ultimately, this project concludes that diclofenac concentrations found in European surface waters are generally below the limits proposed by the WFD, but that exceedances have occasionally been reported in several European countries. In comparison, E2 and EE2 surface water concentrations are generally much lower, though reported values still commonly exceed the WFD proposed limits for these bioactive compounds. Perhaps most notably, while current standard, laboratory-based analytical chemistry methods are sufficiently sensitive for the detection and quantification of diclofenac, the limits of detection for E2 and EE2 are often higher than proposed EQSs. This issue presents serious analytical challenges with regard to chemical monitoring methods and reporting for these two PhACs, and impacts Ireland's ability to meet European reporting requirements. The mapping work conducted during this project demonstrated that more monitoring data on diclofenac, E2 and EE2 in Irish waters are required. Nevertheless, based on the limited Irish data extracted from the literature and mapped in this report, it appears that the majority of Irish surface waters may not exceed WFD proposed limits for diclofenac, E2 and EE2, but

that point sources of pollution could lead to occasional hotspots exceeding European limits. It must be noted that this prediction is based upon the use of very limited data and is especially uncertain because of a lack of sufficiently sensitive analytical detection methods. Finally, the review of control measures conducted during this project determined that diclofenac is poorly removed during conventional wastewater treatment. In contrast, removal percentages for E2 and EE2 are generally 85% or greater using CAS treatment. The advanced treatment options which can further remove these PhACs were evaluated, but best-published literature indicates that the environmental benefits of implementing these solutions may not outweigh the costs.

3.2 Future Research Needs

Future Irish-specific work in this research field is essential in order to ensure PhACs do not threaten our water supplies. In particular, it is important that analytical methods for detecting the steroid oestrogens in waters be optimised and alternatives to chemical analyses, such as biological surrogates or effect-based monitoring techniques, be developed and validated. Irish studies evaluating PhAC levels in WWTP influents and effluents are also lacking; these are needed in order to develop effective and economic control measures for PhAC removal from wastewaters. This report also found that on-site treatment systems could be a major reason for PhAC contamination in an Irish context, so future research should address this issue. Finally, longer term projects that utilise European software and models to predict the fate of watch list compound concentrations in whole Irish watershed areas should be carried out, such as the Geography-Referenced Regional Exposure Assessment Tool for European River Basins (GREAT-ER). The RA model created from this project should be further developed and integrated into such modelling efforts.

4 Recommendations and Policy Implications

1. Advocate for the acceptability of integrative monitoring methods for WFD reporting (short term, EPA and governmental departments)

Currently, the proposed WFD AA EQSs for E2 and EE2 are lower than most limits of detection for standard chemical analyses. This is also a potential problem for other and future watch list substances. Given the positive results and outcomes from studies that utilise effect-based (biological) monitoring, passive sampling or an integrated monitoring approach (combined use of chemical and biological monitoring methods), we recommend that the EPA and Irish government align with other EU Member States that are advocating the acceptance of these types of methodologies for WFD priority substance reporting.

2. Continue funding Irish projects on emerging/established pollutants (short-long term, EPA)

EPA-funded research is currently the only significant source of aquatic monitoring data for watch list compounds in Ireland. We recommend that funding of projects evaluating concentrations in aquatic and other environmental matrices (sludge, sediment, biota) be continued, particularly for compounds that are not yet considered priority substances (current and potential future watch list compounds).

3. Develop and expand the RA model created during this project (short term, EPA)

The RA model developed during this project was designed in line with methodologies approved by the EPA and experts in the field. Additional model development will augment the predictive ability and robustness of this model, and increase the significance and accuracy of its conclusions. Developments of this model could present a unique opportunity to provide a national, singular model for PhAC RA, which can be aligned and compared with other European models and RA research. Extensions of this model could help put Ireland back to the forefront of this research area. Future studies would ideally include a combination of field-based monitoring of PhAC concentrations in influent, effluent and receiving waters (for model validation), as well as further development of the RA model.

4. Identify sources and improve availability of PhAC data (short term, departments and agencies)

This project identified sources of national PhAC consumption (usage) data quickly, but experienced delays in data acquisition. Furthermore, more data should be collected on prescriptions written and dispensed by public and private health agencies in Ireland, and such data should be made available to research projects. Another issue is the unavailability of commercially sensitive data such as PhAC sales/production information. This information would facilitate a more accurate determination of emission sources in different catchments.

5. Consider more than just the parent compound (short term, future research projects)

In order to truly understand the occurrence and resulting environmental impact of PhACs in aquatic matrices, there is a need to measure metabolites, conjugates and transformation products. We recommend that future research considers more than just the parent compound, especially with regard to the compounds of interest.

6. Institute changes to the regulation of pharmaceutical products (long term, departments and agencies)

Currently, pharmaceutical companies do not consider the environmental persistence or recalcitrance of the compounds that they produce. We recommend that changes to this policy be considered, on both national and international levels. Before a product is approved for market, some toxicity testing is typically required, but there is no scenario or mechanism in which the human benefits that come from consumption of a PhAC could be outweighed by negative environmental impact. At a minimum, we recommend that, in addition to toxicity testing, basic evaluations of the environmental persistence of compounds be required in order to bring a new compound to market. In the long term, it may be advisable for RAs of PhACs to include not just risk to the consumer of the product, but environmental risk and persistence as well.

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Abbreviations

AA	Annual average
AC	Activated carbon
CAS	Conventional activated sludge
CW	Constructed wetlands
E2	17-beta-estradiol
EDC	Endocrine disrupting chemical
EE2	17-alpha-ethinylestradiol
EEQ	Estradiol equivalent
EPA	Environmental Protection Agency
EQS	Environmental quality standard
GIS	Geographic information system
GPS	Global Positioning System
LOD	Limit of detection
NSAID	Non-steroidal anti-inflammatory drug
PhAC	Pharmaceutically active chemical
RA	Risk assessment
RBMP	River basin management plan
WFD	Water Framework Directive
WWTP	Wastewater treatment plant

AN GHNÍOMHAIREACHT UM CHAOMHNÚ COMHSHAOL

Tá an Ghníomhaireacht um Chaomhnú Comhshaoil (GCC) freagrach as an gcomhshaoil a chaomhnú agus a fheabhsú mar shócmhainn luachmhar do mhuintir na hÉireann. Táimid tiomanta do dhaoine agus don chomhshaoil a chosaint ó éifeachtaí díobhálacha na radaíochta agus an truaillithe.

Is féidir obair na Gníomhaireachta a roinnt ina trí phríomhréimse:

Rialú: Déanaimid córais éifeachtacha rialaithe agus comhlíonta comhshaoil a chur i bhfeidhm chun torthaí maithe comhshaoil a sholáthar agus chun díriú orthu siúd nach gcloíonn leis na córais sin.

Eolas: Soláthraimid sonraí, faisnéis agus measúnú comhshaoil atá ar ardchaighdeán, spriocdhírthe agus tráthúil chun bonn eolais a chur faoin gcinnteoireacht ar gach leibhéal.

Tacaíocht: Bímid ag saothrú i gcomhar le grúpaí eile chun tacú le comhshaoil atá glan, táirgiúil agus cosanta go maith, agus le hiompar a chuirfidh le comhshaoil inbhuanaithe.

Ár bhFreagrachtaí

Ceadúnú

Déanaimid na gníomhaíochtaí seo a leanas a rialú ionas nach ndéanann siad dochar do shláinte an phobail ná don chomhshaoil:

- saoráidí dramhaíola (*m.sh. láithreáin líonta talún, loisceoirí, stáisiúin aistriúcháin dramhaíola*);
- gníomhaíochtaí tionsclaíoch ar scála mór (*m.sh. déantúsaíocht cógaisíochta, déantúsaíocht stroighne, stáisiúin chumhachta*);
- an diantalmhaíocht (*m.sh. muca, éanlaith*);
- úsáid shrianta agus scaoileadh rialaithe Orgánach Géinmhodhnaithe (*OGM*);
- foinsí radaíochta ianúcháin (*m.sh. trealamh x-gha agus radaiteiripe, foinsí tionsclaíoch*);
- áiseanna móra stórála peitрил;
- scardadh dramhuisce;
- gníomhaíochtaí dumpála ar farraige.

Forfheidhmiú Náisiúnta i leith Cúrsaí Comhshaoil

- Clár náisiúnta iniúchtaí agus cigireachtaí a dhéanamh gach bliain ar shaoráidí a bhfuil ceadúnas ón nGníomhaireacht acu.
- Maoirseacht a dhéanamh ar fhreagrachtaí cosanta comhshaoil na n-údarás áitiúil.
- Caighdeán an uisce óil, arna sholáthar ag soláthraithe uisce poiblí, a mhaoirsiú.
 - Obair le húdaráis áitiúla agus le gníomhaireachtaí eile chun dul i ngleic le coireanna comhshaoil trí chomhordú a dhéanamh ar líonra forfheidhmiúcháin náisiúnta, trí dhírú ar chiontóirí, agus trí mhaoirsiú a dhéanamh ar leasúcháin.
- Cur i bhfeidhm rialachán ar nós na Rialachán um Dhramhthrealamh Leictreach agus Leictreonach (DTLL), um Shrian ar Shubstaintí Guaiseacha agus na Rialachán um rialú ar shubstaintí a ídóinn an ciseal ózóin.
- An dlí a chur orthu siúd a bhriseann dlí an chomhshaoil agus a dhéanann dochar don chomhshaoil.

Bainistíocht Uisce

- Monatóireacht agus tuairisciú a dhéanamh ar cháilíocht aibhneacha, lochanna, uisce idirchriosacha agus cósta na hÉireann, agus screamhuiscí; leibhéal uisce agus sruthanna aibhneacha a thomhas.
- Comhordú náisiúnta agus maoirsiú a dhéanamh ar an gCreat-Treoir Uisce.
- Monatóireacht agus tuairisciú a dhéanamh ar Cháilíocht an Uisce Snámha.

Monatóireacht, Anailís agus Tuairisciú ar an gComhshaoil

- Monatóireacht a dhéanamh ar cháilíocht an aeir agus Treoir an AE maidir le hAer Glan don Eoraip (CAFÉ) a chur chun feidhme.
- Tuairisciú neamhspleách le cabhrú le cinnteoireacht an rialtais náisiúnta agus na n-údarás áitiúil (*m.sh. tuairisciú tréimhsiúil ar staid Chomhshaoil na hÉireann agus Tuarascálacha ar Tháscairí*).

Rialú Astaíochtaí na nGás Ceaptha Teasa in Éirinn

- Fardail agus réamh-mheastacháin na hÉireann maidir le gáis cheaptha teasa a ullmhú.
- An Treoir maidir le Trádáil Astaíochtaí a chur chun feidhme i gcomhair breis agus 100 de na táirgeoirí dé-ocsaíde carbóin is mó in Éirinn.

Taighde agus Forbairt Comhshaoil

- Taighde comhshaoil a chistiú chun brúnna a shainnithint, bonn eolais a chur faoi bheartais, agus réitigh a sholáthar i réimsí na haeraíde, an uisce agus na hinbhuanaitheachta.

Measúnacht Straitéiseach Timpeallachta

- Measúnacht a dhéanamh ar thionchar pleananna agus clár beartaithe ar an gcomhshaoil in Éirinn (*m.sh. mórphleananna forbartha*).

Cosaint Raideolaíoch

- Monatóireacht a dhéanamh ar leibhéil radaíochta, measúnacht a dhéanamh ar nochtadh mhuintir na hÉireann don radaíocht ianúcháin.
- Cabhrú le pleananna náisiúnta a fhorbairt le haghaidh éigeandálaí ag eascairt as taismí núicléacha.
- Monatóireacht a dhéanamh ar fhorbairtí thar lear a bhaineann le saoráidí núicléacha agus leis an tsábháilteacht raideolaíochta.
- Sainseirbhísí cosanta ar an radaíocht a sholáthar, nó maoirsiú a dhéanamh ar sholáthar na seirbhísí sin.

Treoir, Faisnéis Inrochtana agus Oideachas

- Comhairle agus treoir a chur ar fáil d'earnáil na tionsclaíochta agus don phobal maidir le hábhair a bhaineann le caomhnú an chomhshaoil agus leis an gcosaint raideolaíoch.
- Faisnéis thráthúil ar an gcomhshaoil ar a bhfuil fáil éasca a chur ar fáil chun rannpháirtíocht an phobail a spreagadh sa chinnteoireacht i ndáil leis an gcomhshaoil (*m.sh. Timpeall an Tí, léarscáileanna radóin*).
- Comhairle a chur ar fáil don Rialtas maidir le hábhair a bhaineann leis an tsábháilteacht raideolaíoch agus le cúrsaí práinnfhreagartha.
- Plean Náisiúnta Bainistíochta Dramhaíola Guaisí a fhorbairt chun dramhaíl ghuaiseach a chosc agus a bhainistiú.

Múscailt Feasachta agus Athrú Iompraíochta

- Feasacht chomhshaoil níos fearr a ghiniúint agus dul i bhfeidhm ar athrú iompraíochta dearfach trí thacú le gnóthais, le pobail agus le teaghlaigh a bheith níos éifeachtúla ar acmhainní.
- Tástáil le haghaidh radóin a chur chun cinn i dtithe agus in ionaid oibre, agus gníomhartha leasúcháin a spreagadh nuair is gá.

Bainistíocht agus struchtúr na Gníomhaireachta um Chaomhnú Comhshaoil

Tá an ghníomhaíocht á bainistiú ag Bord lánaimseartha, ar a bhfuil Ard-Stiúrthóir agus cúigear Stiúrthóirí. Déantar an obair ar fud cúig cinn d'Oifigí:

- An Oifig um Inmharthanacht Comhshaoil
- An Oifig Forfheidhmithe i leith cúrsaí Comhshaoil
- An Oifig um Fianaise is Measúnú
- An Oifig um Cosaint Raideolaíoch
- An Oifig Cumarsáide agus Seirbhísí Corparáideacha

Tá Coiste Comhairleach ag an nGníomhaireacht le cabhrú léi. Tá dáréag comhaltaí air agus tagann siad le chéile go rialta le plé a dhéanamh ar ábhair inní agus le comhairle a chur ar an mBord.

Investigation of the Implications for Ireland of Emerging Standards on Pharmaceuticals in Receiving Waters



Authors: Erin Jo Tiedeken, Eoghan Clifford and Neil J. Rowan

Water is crucial for all living organisms and for human activities. This report investigates the implications for Ireland of diclofenac (an anti-inflammatory drug, DCL), 17-beta-estradiol (natural estrogenic hormone, E2) and 17-alpha-ethynylestradiol (synthetic estrogenic hormone, EE2) that were added to the EU “watch list” in 2013. These pharmaceutical compounds mainly enter waterways via human use of medications, followed by excretion and incomplete removal at conventional wastewater treatment plants (WWTPs). The impacts of chronic exposure to trace concentrations of these biologically-active pharmaceuticals on aquatic wildlife and human health may be severe; studies in an Irish context are required to understand this issue, and for benchmarking with other EU countries.

This report provides an understanding of the state of research on three emerging aquatic pollutants of particular legislative importance, and demonstrates the need to protect our waterways from the severe anthropogenic pressure of chemical pollutants.

Identifying Pressures

While current laboratory-based analytical chemistry methods are sufficiently sensitive for the detection and quantification of diclofenac, increased sensitivity is required for detecting E2 and EE2. An EU-wide database was created on this topic after screening approximately 4,000 published references over a 20-year period. In order to evaluate the mobility of Pharmaceutical Active Chemicals (PhACs) in an Irish context, existing Irish data were collated and used to map monitoring locations, frequency, and where possible, concentrations of the compounds that exceed proposed environmental quality standards (EQS). The majority of Irish surface waters do not exceed WFD-proposed EQS for diclofenac. However, hot spots occasionally occur for E2 and EE2 which is not surprising as the WFD EQS limits set for these estrogens are below the capabilities of conventional monitoring techniques. This project created a semi-quantitative baseline risk assessment model for helping to identify potentially hot spot WWTPs for greater monitoring and mitigation.

Informing Policy

The “watch list” initially comprising these three pharmaceutical compounds was created by Article 8b of Directive 2013/39/EU, which was then expanded to 10 substances under EU Commission Decision 2015/485. Watch list substances must be monitored for the purpose of supporting future prioritisation exercises. This recent legislation was identified as a potentially significant water management issue for consideration in the second round of Irish River Basin Management Plans (due for publication in 2017). This project provides a baseline study for Ireland on the implications of these three PhACs to future priority substances lists.

Developing Solutions

The findings from this research provide information and recommendations to aid in informed decision making regarding an increasingly important class of emerging pollutants. A review of treatment options effective for removal of diclofenac, E2 and EE2 was undertaken and a toolkit was developed to further aid decision-making. A critical understanding of treatment measures in an Irish context, as provided by this report, is imperative if these compounds are added to future priority substances lists.

