Investigation of the implications for Ireland of emerging standards on pharmaceuticals in receiving waters

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Background

- Pollution of European receiving waters with contaminants of emerging concern (CECS), such as with 17-beta-estradiol (a natural estrogenic hormone, E2), along with pharmaceutically-active compounds diclofenac (an anti-inflammatory drug, DCL) and 17-alpha-ethynylestradiol (a synthetic estrogenic hormone, EE2)) is a ubiquitous phenomenon.
- These three CECS were added to the EU watch list of emerging substances to be monitoring in 2013, which was updated in 2015 to comprise 10 substances/groups of substances in the field of water policy.
- Anticipate their entrance in the **water framework directive (WFD)** priority subtances list
- Complex problem on many levels suggesting that we are dealing with this problem from crisis management perspective - but need to move towards prevention – we need to understand situation by way of monitored data and share this openly.

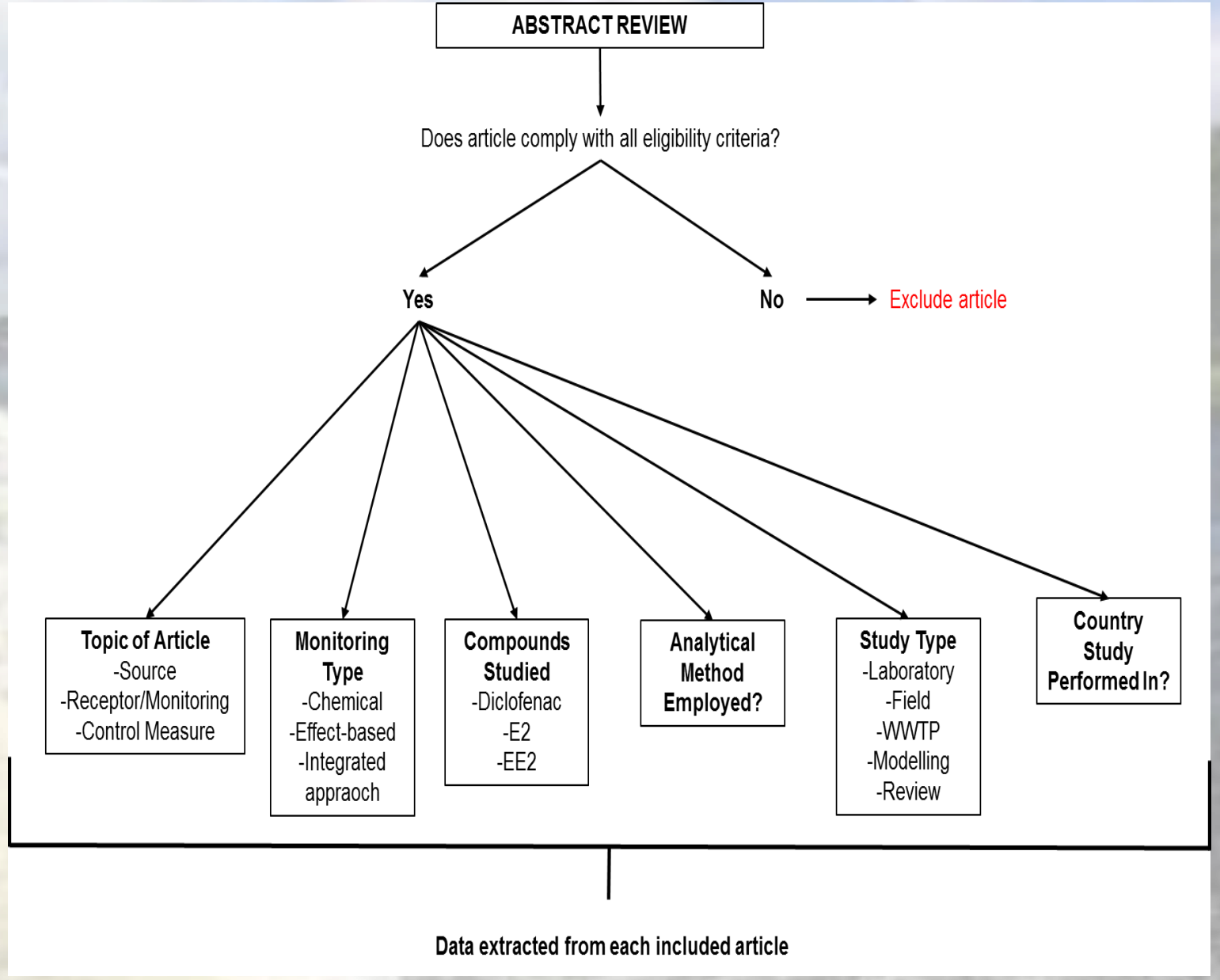
Project objectives

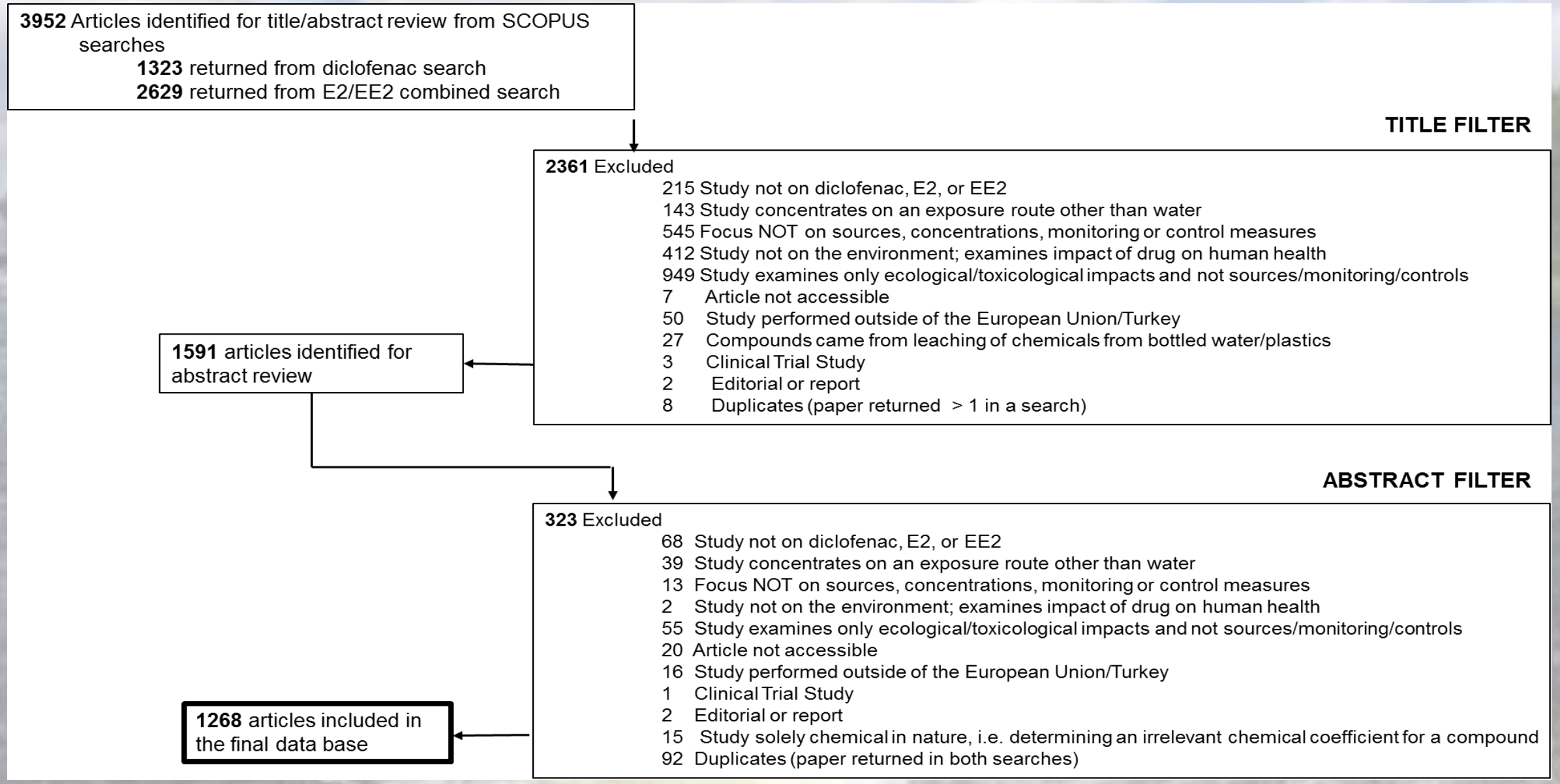
- To ascertain positioning of Ireland as it relates to other EU countries for information on monitoring, sources, receptors and control measures for diclofenac (DCL), E2 and EE2 from 1995 to 2015
- To map locations and concentrations of DCL, E2 and EE2 in Irish receiving waters from 1999-2014
- To develop semi-quantitative risk assessment (RA) model to predict at risk wastewater treatment plants in Ireland in order to inform future research and decision-making for policy.

Eligibility criteria for **systematic literature review**; used for title and abstract filter.

Eligibility Criteria
- Must specifically discuss at least one of the three compounds of interest - Cannot focus exclusively on impacts of compound for human/animal/plant health - Exclude papers that focus only on ecological/environmental/toxicological impacts unless they also discuss relevant sources, receptors/monitoring or control measures - Exclude clinical trial studies - Must include some specific information on sources, receptors/monitoring or control measures - Cannot focus on exposure routes other than water - Study cannot be purely chemical, i.e. determining a chemical coefficient - Exclude any papers on leaching of chemicals from bottled water/plastics - Must be peer reviewed original article or review, or article in press - Must be published between 1995-May 2015 - Research must be conducted in Europe or by at least one author affiliated with a European country - Article must be written in English - Full text must be available

A systematic literature review was conducted of 3,952 potentially relevant articles over period 1995 to 2015 that produced a new EU-wide database consisting of 1,268 publications on DCL, E2 and EE2.




3952 Articles identified for title/abstract review from SCOPUS searches
1323 returned from diclofenac search
2629 returned from E2/EE2 combined search
TITLE FILTER
2361 Excluded
215 Study not on diclofenac, E2, or EE2
143 Study concentrates on an exposure route other than water
545 Focus NOT on sources, concentrations, monitoring or control measures
412 Study not on the environment; examines impact of drug on human health
949 Study examines only ecological/toxicological impacts and not sources/monitoring/controls
7 Article not accessible
50 Study performed outside of the European Union/Turkey
27 Compounds came from leaching of chemicals from bottled water/plastics
3 Clinical Trial Study
2 Editorial or report
8 Duplicates (paper returned > 1 in a search)
1591 articles identified for abstract review
ABSTRACT FILTER
323 Excluded
68 Study not on diclofenac, E2, or EE2
39 Study concentrates on an exposure route other than water
13 Focus NOT on sources, concentrations, monitoring or control measures
2 Study not on the environment; examines impact of drug on human health
55 Study examines only ecological/toxicological impacts and not sources/monitoring/controls
20 Article not accessible
16 Study performed outside of the European Union/Turkey
1 Clinical Trial Study
2 Editorial or report
15 Study solely chemical in nature, i.e. determining an irrelevant chemical coefficient for a compound
92 Duplicates (paper returned in both searches)
1268 articles included in the final data base

Search	Original combined order	Unique identifier	Order_ Newest _Oldest	Title	Abstract	Source	Receptor /monitoring	Control measure	Concentration or effect study	Notes	Diclofenac studied	E2 studied	EE2 studied	Additional chemicals	Analytical method employed for detection	Data for extraction	Type of study	Country study performed in	Authors	Year	Source title	Volume	Issue	Art. No.	Page start	Page end	Page count	Cited by	DOI	Link	Affiliations	Authors with affiliations	Author Keywords	Index Keywords	Molecular Sequence Numbers	Chemicals/ CAS	Tradenames	Manufacturers	Funding Details	Correspondence Address	Language of Original Document	Document Type	Source	EID
diclofenac	45	1268	81	Removal of endocrine dis	Endocrine	1	0	1	concentration		1	1	1	1	NS	1	WWTP	Greece	Noutsopo	2015	Chemospl	119			S109	S114		10.1016/j.	http://ww	Sanitary Eng	Noutsopou	By-product	Biological materials; Byprc	chlorine, 13981-72-1, 7782-50-5; humic acid, 1415-93-				Noutsopoulos, C.,	English	Article	Scopus	2-s2.0-84922721898
diclofenac/E2/E	44	1267	80	Pharmaceuticals in groun	The major	1	1	0	concentration		1	1	1	1	NS	0	review	Czech Republic	Rozman D	2015	Environm	73	7		3775	3784		10.1007/s	http://ww	T.G. Masaryl	Rozman, D.	Groundwat	Drug dosage; Drug products; Groundwater; Groundwater pollution; Hospitals; Ir				Rozman, D., T.G. M	English	Article	Scopus	2-s2.0-84924664642
diclofenac	43	1266	79	Advanced treatment of ur	Pharmace	0	0	1	concentration		1	0	0	1	NS	1	lab	Italy	Rizzo L., Fi	2015	Journal of	3	1		122	128		10.1016/j.	http://ww	Department	Rizzo, L., De	Agricultura	Activated carbon; Adsorption; Carbon; Carbon nanotubes; Drug products; Granu				Rizzo, L., Departm	English	Article	Scopus	2-s2.0-84920461510
diclofenac	42	1265	78	Toward the development	New resul	0	0	1	concentration		1	0	0	1	NS	1	lab	Greece	Sklari S.D.	2015	Industrial	54	7		2059	2073		10.1021/ie	http://ww	Chemical Pr	Sklari, S.D.,	Chemical P	Carbon; Cathodes; Dissolved oxygen; Felt; Iron; Iron compounds; Organic chemi				Karabelas, A.J.; Cl	English	Article	Scopus	2-s2.0-84923482221
diclofenac	41	1264	76	Enhanced ozonation of se	In search	0	0	1	concentration		1	0	0	1	NS	1	lab	Italy/Turkey	Naddeo V	2015	Environm	36	15		1876	1883		10.1080/0	http://ww	Sanitary Env	Naddeo, V.	advanced oxidation processes; degradation; emerging contaminants; ozone; ultrasound				Naddeo, V., Sanit	English	Article	Scopus	2-s2.0-84929291361
diclofenac	40	1263	74	Is there a risk for the aqua	The ecolo	1	1	0	concentration		1	1	1	1	NS	1	field	Greece	Thomaidi	2015	Journal of	283			740	747		10.1016/j.	http://ww	Department	Thomaidi, I	Effects; Env	Algae; Aquatic organisms;	4,4' isopropylidenediphenol, 80-05-7; amoxicillin, 26			Stasinakis, A.S.; D	English	Article	Scopus	2-s2.0-84920066230
diclofenac	39	1262	73	Lab-scale experimental st	The nitrify	1	0	1	concentration		1	0	0	1	NS	1	WWTP	France	Pomies M	2015	Environm	22	6		4383	4395		10.1007/s	http://ww	Irstea, UR M	Pomiès, M.	Activated sludge; Experimental strategy; Modelling; Pharmaceuticals; Wastewater treatme				Choubert, J.M.; Ir	English	Article	Scopus	2-s2.0-84925465429
diclofenac	38	1261	71	Impacts of coagulation on	The applic	1	0	1	concentration		1	0	0	1	NS	1	WWTP	Germany	Altmann J	2015	Chemospl	125			198	204		10.1016/j.	http://ww	Technische I	Altmann, J.	Coagulatio	Activated carbon; Activate activated carbon, 64365-11-3, 82228-96-4; carbamaze				Altmann, J.; Techi	English	Article	Scopus	2-s2.0-84923578334
diclofenac	37	1259	70	Identification of some fac	Many tech	1	0	1	concentration		1	0	0	1	NS	1	WWTP	Spain	Badia-Fab	2015	Journal of	283			663	671		10.1016/j.	http://ww	Departamer	Badia-Fabr	Deconjugat	Drug products; Deconjugal	atenolol, 29122-68-7, 93379-54-5; carbamazepine, 29			Caminal, G.; Instit	English	Article	Scopus	2-s2.0-84910045461
E2/EE2	601	1260	70	Comprehensive two-dime	For the fir	1	1	0	concentration		0	1	0	1	two-dimens	1	lab	The Netherlands	Ouyang X.	2015	Journal of	1380			139	145		10.1016/j.	http://ww	Institute for	Ouyang, X.,	Compreher	Aromatic hydrocarbons; Cl	amitriptyline, 50-48-6, 549-18-8; bigeriden, 1235-82-1			Ouyang, X., Instit	English	Article	Scopus	2-s2.0-84921323262
diclofenac	36	1258	69	Influence of wastewater p	In this Arti	1	0	1	concentration		1	0	0	1	NS	0	lab	Germany	Zucker I.,	2015	Environm	49	1		301	308		10.1021/e	http://ww	School of M	Zucker, I.,	School of Me	Biological materials; Cont	carbamazepine, 298-46-4, 8047-84-5; diclofenac, 153(			Mamane, H.; Schc	English	Article	Scopus	2-s2.0-84924978088
diclofenac	35	1257	67	Are WWTPs effluents resp	Adverse e	1	1	0	concentration/effec		1	0	0	1	NS	0	field	Spain	Maranho L	2015	Ecotoxicol	24	2		368	380		1 10.1007/s	http://ww	Physical Che	Maranho, L	Acute bioa	amitriptyline; atenolol; az	amitriptyline, 50-48-6, 549-18-8; atenolol, ; BEK 0362/			Maranho, L.A.; Ph	English	Article	Scopus	2-s2.0-84925501570
diclofenac	34	1256	66	Impact of in-sewer transfo	The occur	1	0	1	concentration		1	0	0	1	NS	1	WWTP	Spain	Jelic A., Re	2015	Water Res	68			98	108		1 10.1016/j.	http://ww	Catalan Insti	Jelic, A., Ca	Pharmaceu	Wastewater, Anaerobic co	amlodipine, 88150-42-9; 103129-82-4, 736178-83-9; at			Rodriguez-Mozaz	English	Article	Scopus	2-s2.0-84908408988
diclofenac	33	1255	65	Current anthropogenic pr	Coastal wa	0	1	0	concentration		1	0	0	1	LC-MS	0	field	Spain	Pascual-A	2015	Science of	503-504			90	199		10.1016/j.	http://ww	Centro de In	Pascual-Ag	Anthropoge	Anthropogenic pressures;	carbamazepine, 298-46-4, 8047-84-5; ciprofloxacin, 8			Pascual-Aguilar, J	English	Article	Scopus	2-s2.0-84909981733
E2/EE2	600	1254	64	Impact of an estrogenic se	Despite ef	0	1	0	effect	Tests for e	0	1	1	1	NA	0	lab	Germany	Schneider	2015	Journal of	50	3		272	281		10.1080/1	http://ww	Goethe Univ	Schneider,	Artificial in	Effluent treatment; Endoc	estradiol, 50-28-2			Schneider, I.; Goe	English	Article	Scopus	2-s2.0-84921324517
diclofenac	32	1253	62	Selection of organic proce	An increas	1	1	0	concentration		1	0	0	1	NA	0	review	Germany	Jekel M., J	2015	Chemospl	125			155	167		10.1016/j.	http://ww	Centre for W	Jekel, M., C	Aquatic em	Activated carbon; Agricult	acesulfame, 33665-90-6, 55589-62-3; activated carbor			Ruhl, A.S.; Centre	English	Article	Scopus	2-s2.0-84923384281
diclofenac	31	1252	57	Multi-residue analysis of p	Through s	1	0	1	concentration		1	0	0	1	liquid chror	1	WWTP	Belgium	Vergeynst	2015	Chemospl	119			S2	S8		1 10.1016/j.	http://ww	Research Gr	Vergeynst,	Emerging p	Bioreactors; Chromatogra	diclofenac, 15307-79-6, 15307-86-5; venlafaxine, 934(			Demeestere, K.; F	English	Article	Scopus	2-s2.0-84922693681
diclofenac	30	1251	55	Effect of temperature on t	This study	0	0	1	concentration		1	0	0	1	NS	0	lab	Germany	Alidina M.	2015	Chemospl	122			23	31		1 10.1016/j.	http://ww	Water Reusi	Alidina, M.,	LC-MS/MS;	Aquifers; Chemicals; Envir	diclofenac, 15307-79-6, 15307-86-5; gemfibrozil, 258(			Drewes, J.E.; Chai	English	Article	Scopus	2-s2.0-84920531613
diclofenac	29	1250	54	Environmental impact of p	The occur	1	0	1	concentration		1	0	0	1	LC-MS-MS	1	WWTP	Portugal	Pereira A.	2015	Environm	136			108	119		10.1016/j.	http://ww	Group of He	Pereira, A.I	Environmer	alprazolam; azithromycin;	alprazolam, 28981-97-7; azithromycin, 83905-01-5; be			Silva, L.J.G., Grou	English	Article	Scopus	2-s2.0-84911438964

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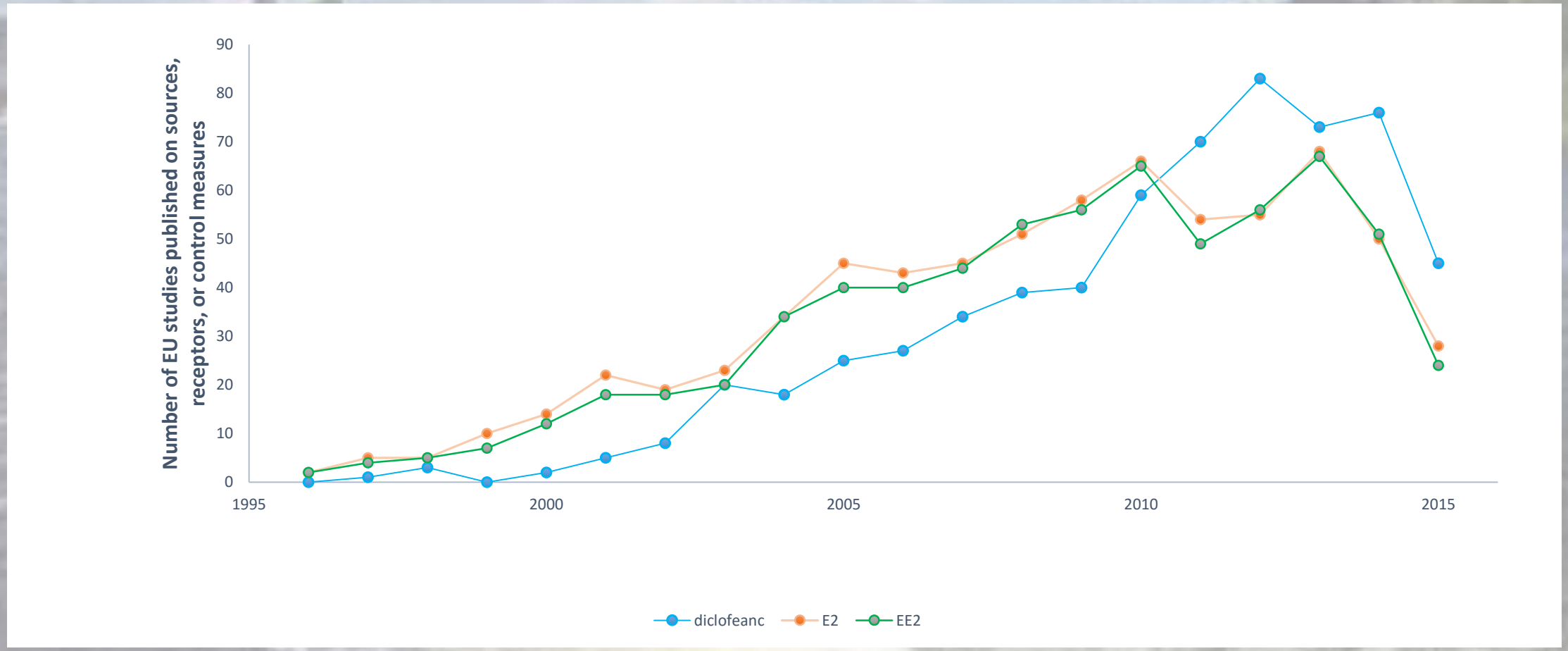
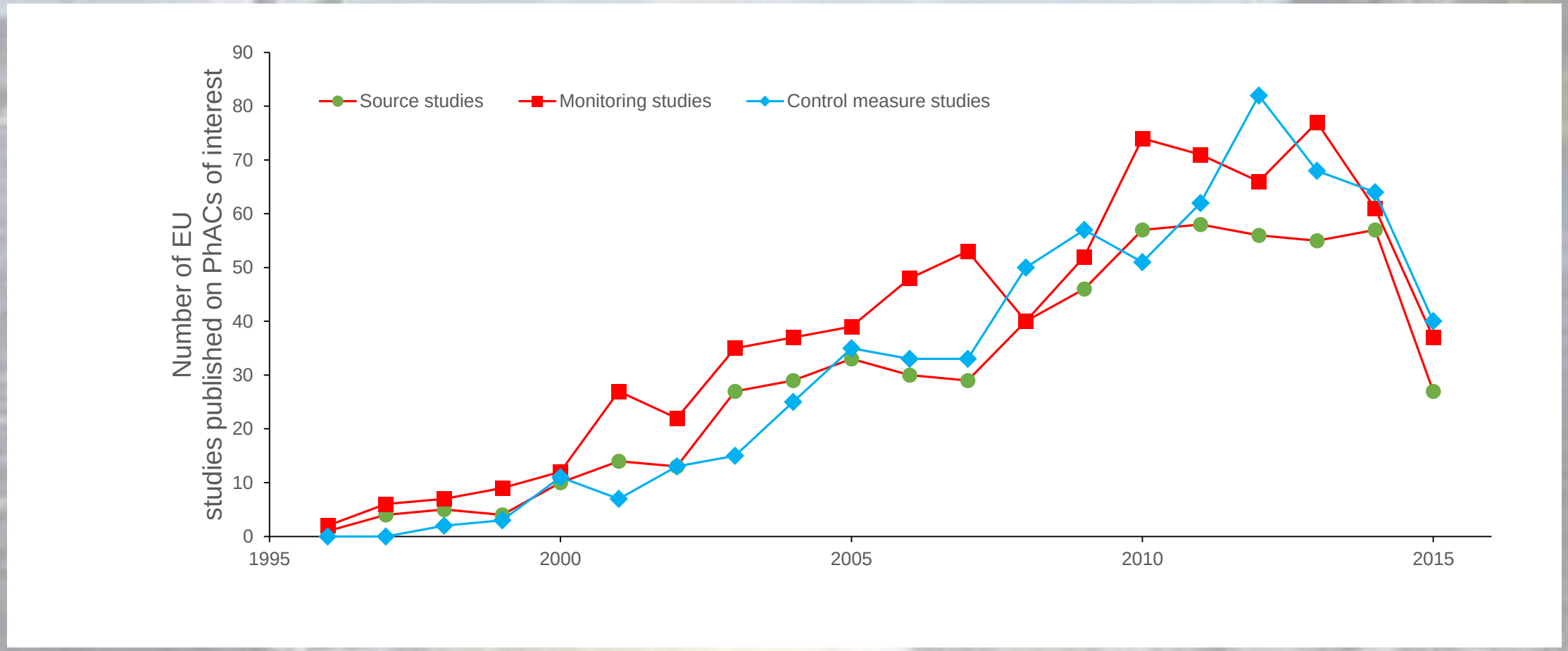
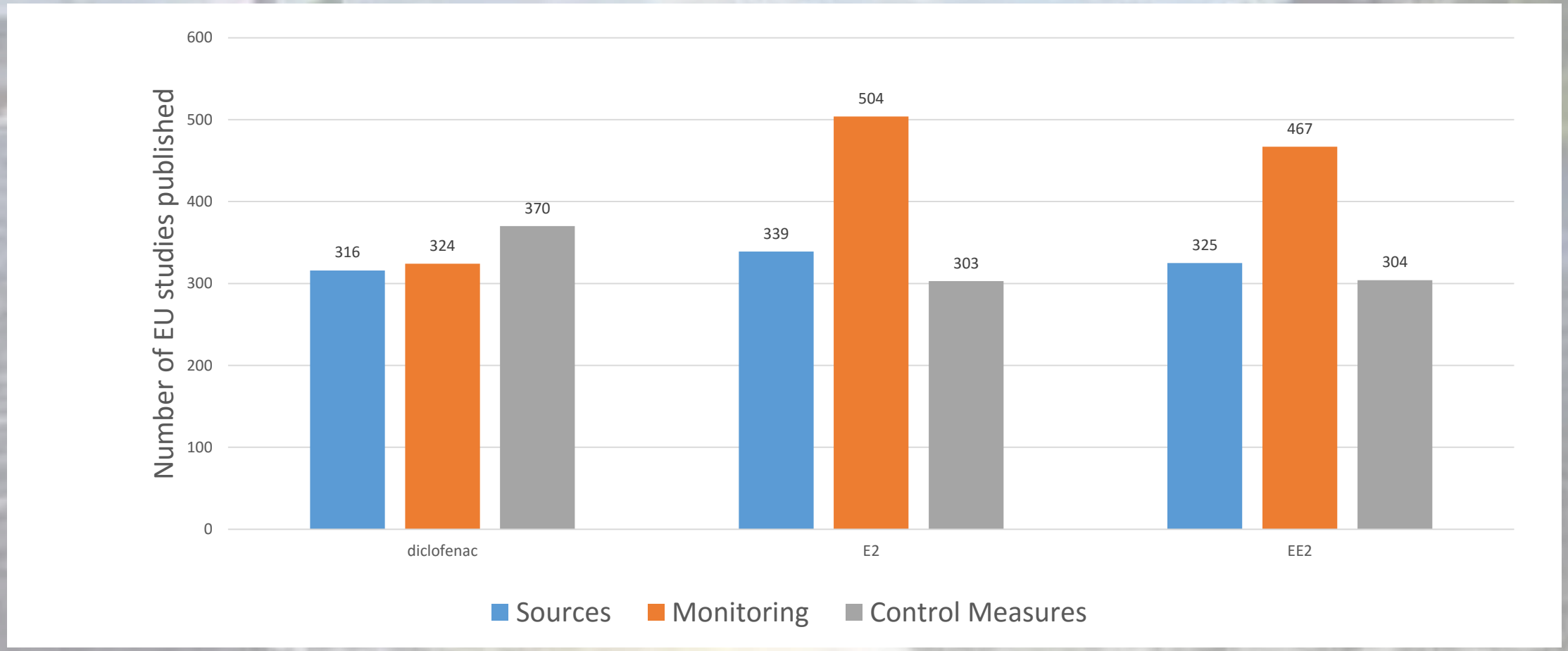
Total combined number of EU studies on sources, receptors or control measures for each DCL , E2 and EE2 from 1995-May 2015, by year



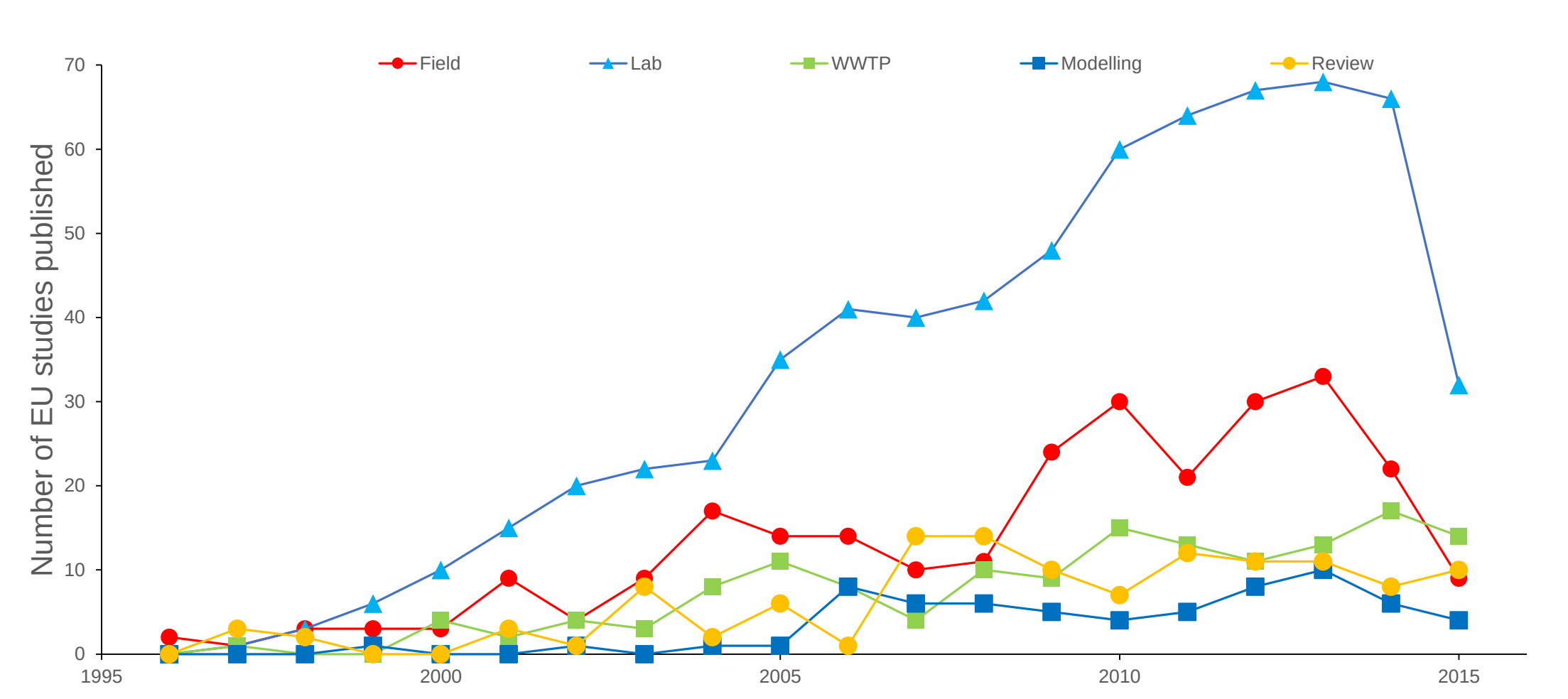
Number of EU studies on at least one of the three pharmaceuticals of interest (DCL, E2 or EE2) investigating: sources of contamination, monitoring data or techniques , or control measures, from 1995-May 2015, by year



Total number of EU studies on each pharmaceutical of interest investigating sources, of contamination, monitoring data or techniques, or control measures, from 1995-May 2015.



Number of studies on three CECs (DCL, E2 and/or EE2) published in the EU from 1995-May 2015 broken down by type of study: field, laboratory scale, WWTP, modelling and review.



EU country research outputs on DCL, E2 and/or EE2

- WHY DO BIBLIOGRAPHIC ANALYSIS AND SYSTEMIC REVIEW?

- FINDINGS FROM EU-WIDE STUDIES OVER 20 YEAR PERIOD USED TO SUPPORT RA MODEL DEVELOPMENT

- IDENTIFY GAPS IN KNOWLEDGE MAJOR BOTTLENECKS
  -ACCESSING DATA FROM HEALTH BOARDS, PHARMACEUTICAL COMPANIES
  -REPITATION AND QUALITY OF DATA – NO SHARED REPOSITORY (ICT – BIG DATA) = NATIONAL/EU-WIDE

Country	Total number (%) of Studies
Spain	285 (19.2)
Germany	243 (16.3)
United Kingdom	179 (12.0)
France	93 (6.3)
Switzerland	87 (5.8)
Italy	84 (5.7)
The Netherlands	57 (3.8)
Sweden	51 (3.4)
Portugal	50 (3.4)
Greece	43 (2.9)
Belgium	42 (2.8)
Denmark	37 (2.5)
Poland	37 (2.5)
Czech Republic	26 (1.7)
Austria	24 (1.6)
Finland	23 (1.5)
Norway	21 (1.4)
Slovenia	21 (1.4)
Turkey	19 1.3)
Ireland	17 (1.2)
Cyprus	14 (0.9)
Hungary	11 (0.7)
Romania	7 (0.5)
Luxembourg	6 (0.4)
Croatia	3 (0.2)
Slovakia	3 (0.2)
Bulgaria	2 0.1)
Estonia	2 (0.1)
Northern Ireland	2 (0.1)
Lithuania	1 (0.06)
Latvia	0 (0)
Malta	0 (0)

Some observations – from 20 year bibliographic analysis and review

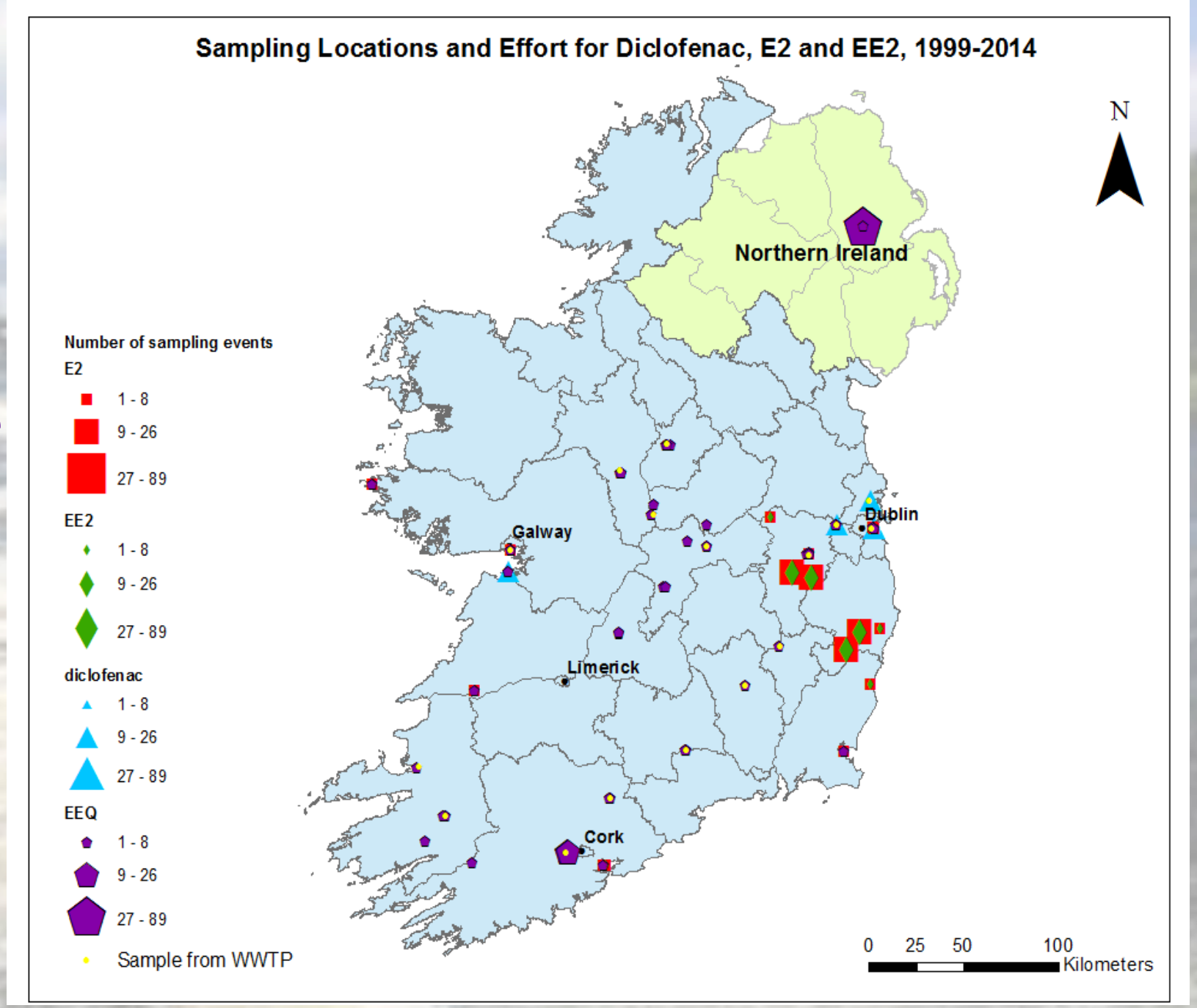
- European surface water concentrations of DCL are typically reported below the proposed annual average environmental quality standard (AA EQS) of 100 ng/l, but that exceedances frequently occur.
- E2 and EE2 surface water concentrations are typically below 50 ng/l and 10 ng/l respectively, but these values greatly exceed the proposed AA EQS values for these compounds (0.04 and 0.035 ng/l respectively). However, levels of these CECs are frequently reported to be disproportionately high in EU receiving waters, particularly in effluents at control points that require urgent attention.
- Overall it was found that DCL and EE2 enter European aquatic environment mainly following human consumption and excretion of therapeutic drugs, and by incomplete removal from influent at urban wastewater treatment plants (WWTPs).
- Current conventional analytical chemistry methods are sufficiently sensitive for the detection and quantification of DCL but not for E2 and EE2, thus alternative, ultra-trace, time-integrated monitoring techniques such as passive sampling are needed to inform water quality for these estrogens.
- DCL appears resistant to conventional wastewater treatment while E2 and EE2 have high removal efficiencies that occurs through biodegradation or sorption to organic matter.

GIS mapping of DCL, E2 and EE2 occurrence in Irish Receiving Waters

- Date water samples were taken including day, month and year
- Type of study measuring concentration for DCL, E2, EE2 or estradiols equivalents (EEQ)
- Method of sampling (grab, passive) + Matrix studied (marine water,lake water, ground, effluent etc)
- GPS coordinates for sampling location identified both in WGS84 and Irish National Grid using publications or reverting to author
- Location of WWTPs – via EPA via primary discharge licence
- Concentration (ng/L recorded) for each sampling event
- If multiple samples taken at same location then each sampling event recorded separately
- Two aspects of data mapped – distribution of sampling events and concentration of each compound at location
- In order to map sampling events – data divided into 1999-2004, 2005-2009, 2010-2014
- Data mapped using ArcGIS Desktop software – a geodatabase was created with sampling data from previous publications were read into ArcMap as .csv tables and exported as shapefiles for full functionality
- Data on human population distribution were downloaded from Central Statistics Office “StatBank Ireland” including country boundaries, city locations, population density
- EPA’s Geo Portal utilised for river basin catchments, WFD river basin districts, WWTP locations and attribute data, and WFD protected areas

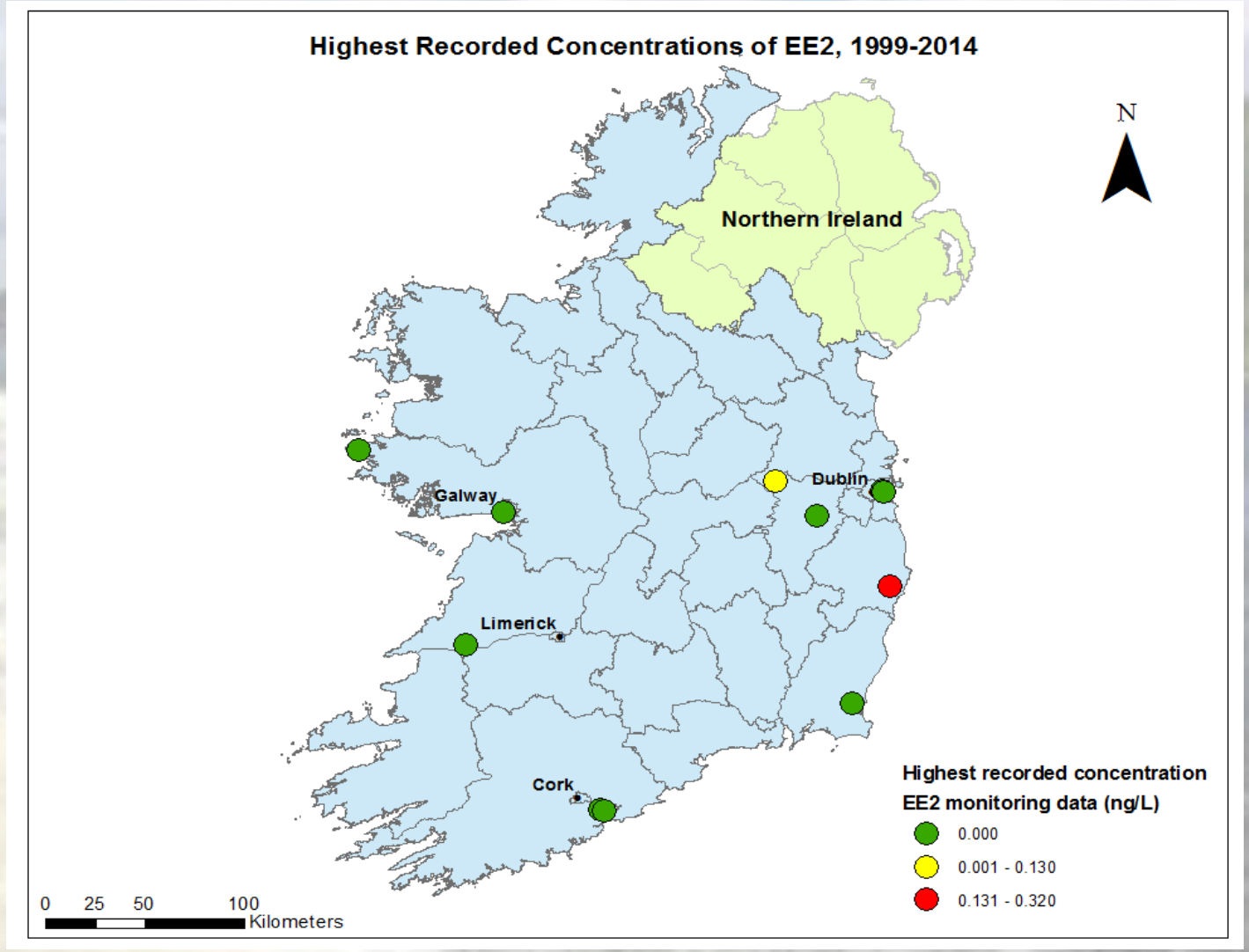
Summary of national monitoring distribution and frequency for:
diclofenac (blue triangles),
E2 (red squares),
EE2 (green diamonds),
estradiols equivalents (purple pentagons) in Ireland from 1999-2014.

Symbol size increases with increasing number of samples taken at each location.



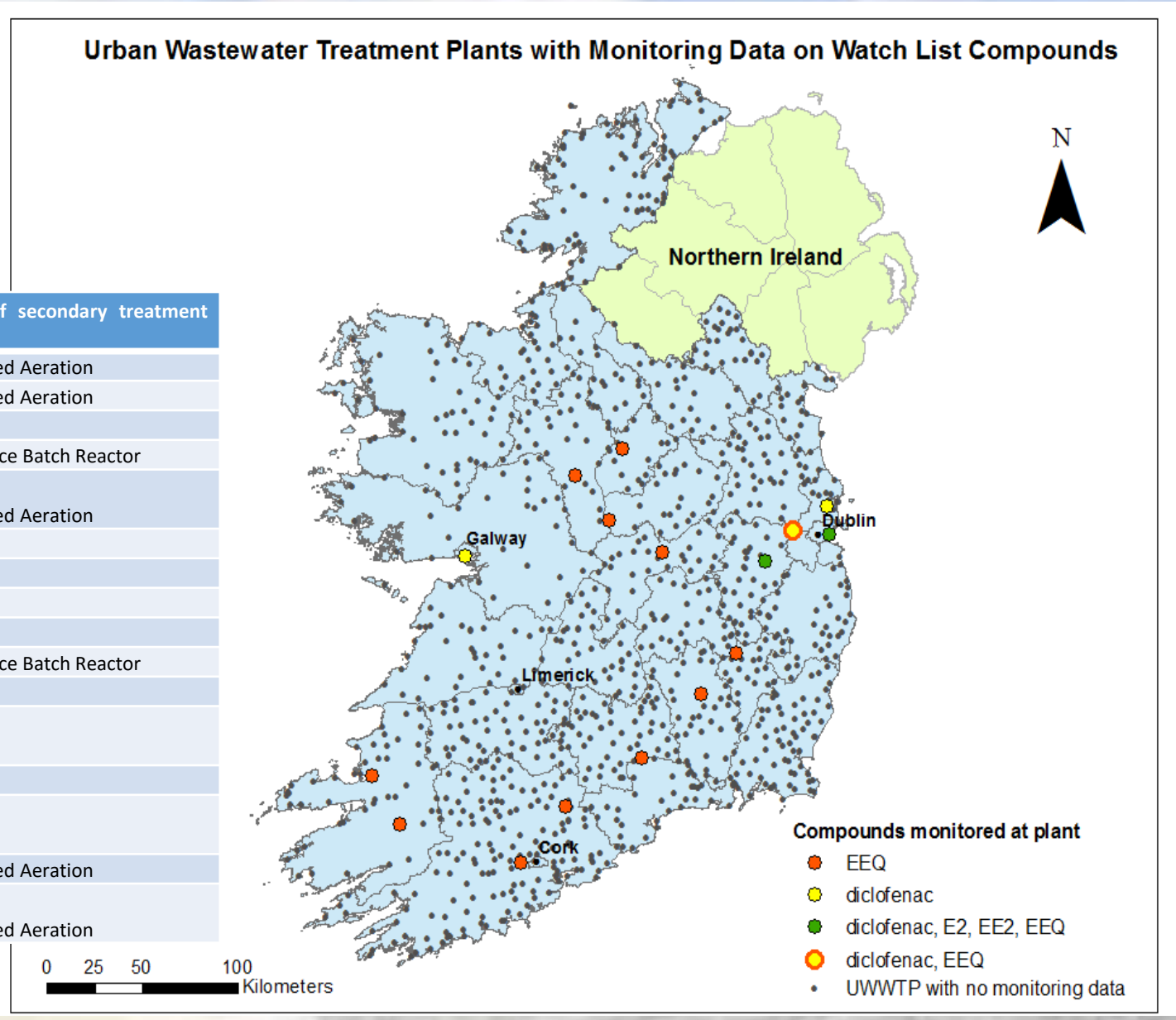
EXAMPLE

Highest recorded concentrations (ng/l) of EE2 at each sampling site 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.



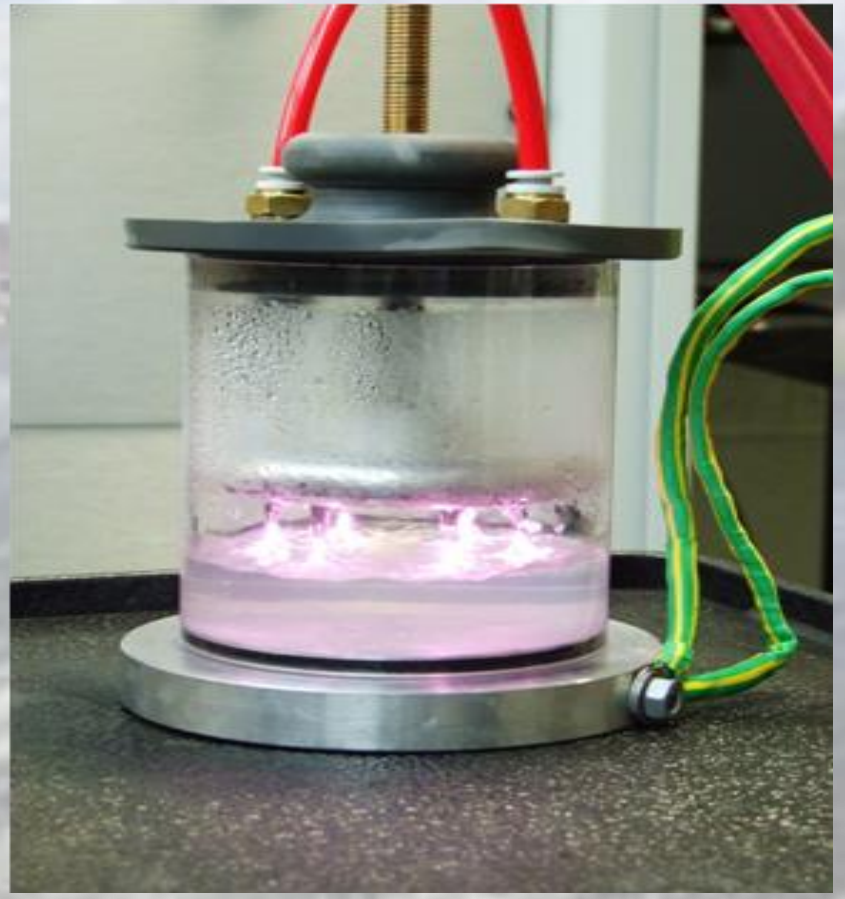
Distribution of urban wastewater treatment plants (UWWTPs) with existing monitoring data on diclofenac, EE2 and/or estradiol equivalents (EEQ).

WWTP name	County	Catchment	WFD river basin district	Size (PE)	Type of secondary treatment (final)
Carlow	Carlow	Barrow	South-eastern	39043	Extended Aeration
Ballincollig	Cork	Lee	South-western	27697	Extended Aeration
Fermoy	Cork	Blackwater	South-western	18608	CAS
Ringsend	Dublin	Coastal	Eastern	2124000	Sequence Batch Reactor
Swords	Fingal	Broad Meadow Water	Eastern	77014	Extended Aeration
Galway	Galway	Coastal	Western	213424	CAS
Killarney	Kerry	Laune	South-western	41836	CAS
Tralee	Kerry	Coastal	Shannon	35149	CAS
Leixlip	Kildare	Liffey	Eastern	100309	CAS
Osberstown	Kildare	Liffey	Eastern	104723	Sequence Batch Reactor
Kilkenny	Kilkenny	Nore	South-eastern	51988	CAS
Longford	Longford	Shannon Upper	Shannon	11672	CAS
Tullamore	Offaly	Shannon Lower	Shannon	24055	CAS
Roscommon	Roscommon	Shannon Upper	Shannon	6989	CAS
Clonmel	Tipperary	Suir	South-eastern	34909	Extended Aeration
Athlone	Westmeath	Shannon Upper	Shannon	21155	Extended Aeration



McGee, C., Brougham, J., Roche, J., Fogarty, A. (2012). First report of intersex roach residing in Irish rivers downstream of several wastewater treatment plants. Royal Irish Academy, Vol 112B, No. 1, pp 69-77.

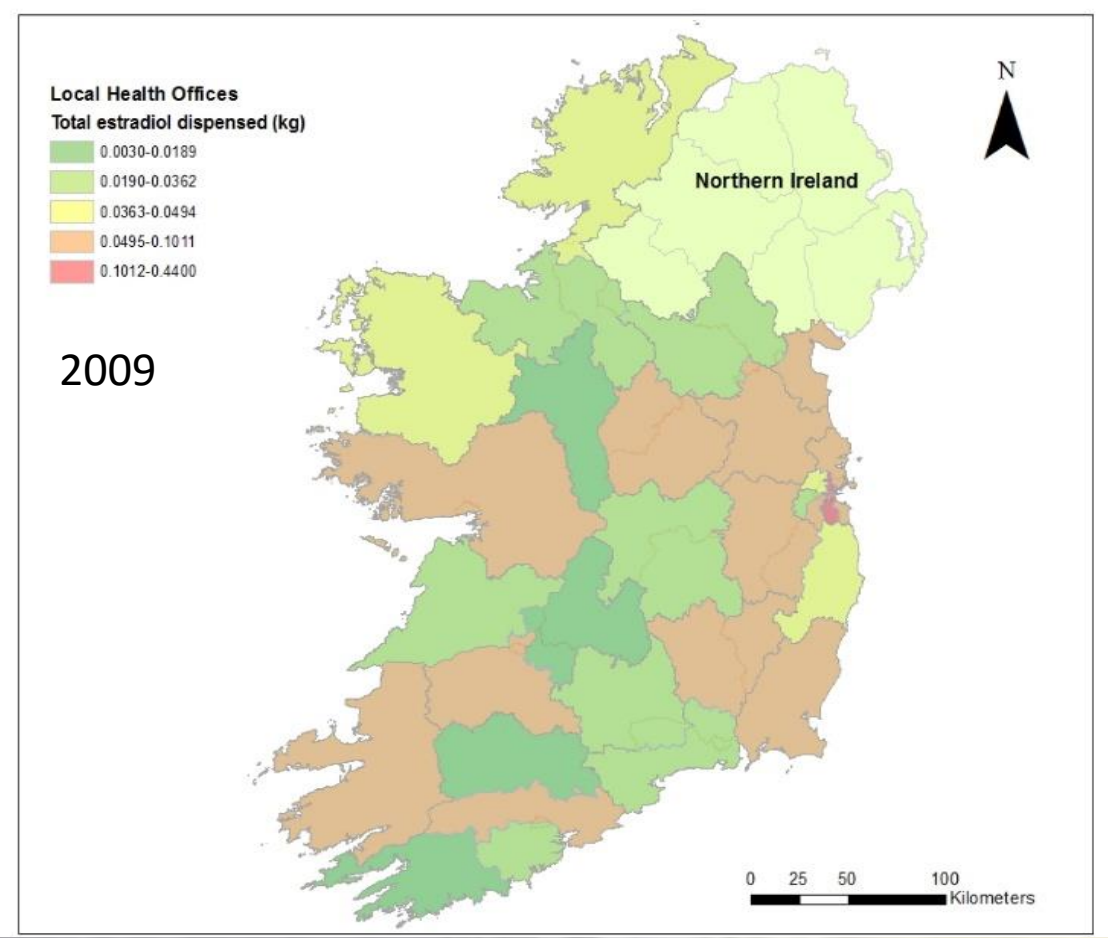
Pilot tertiary treatment facility at WWTP - Ireland



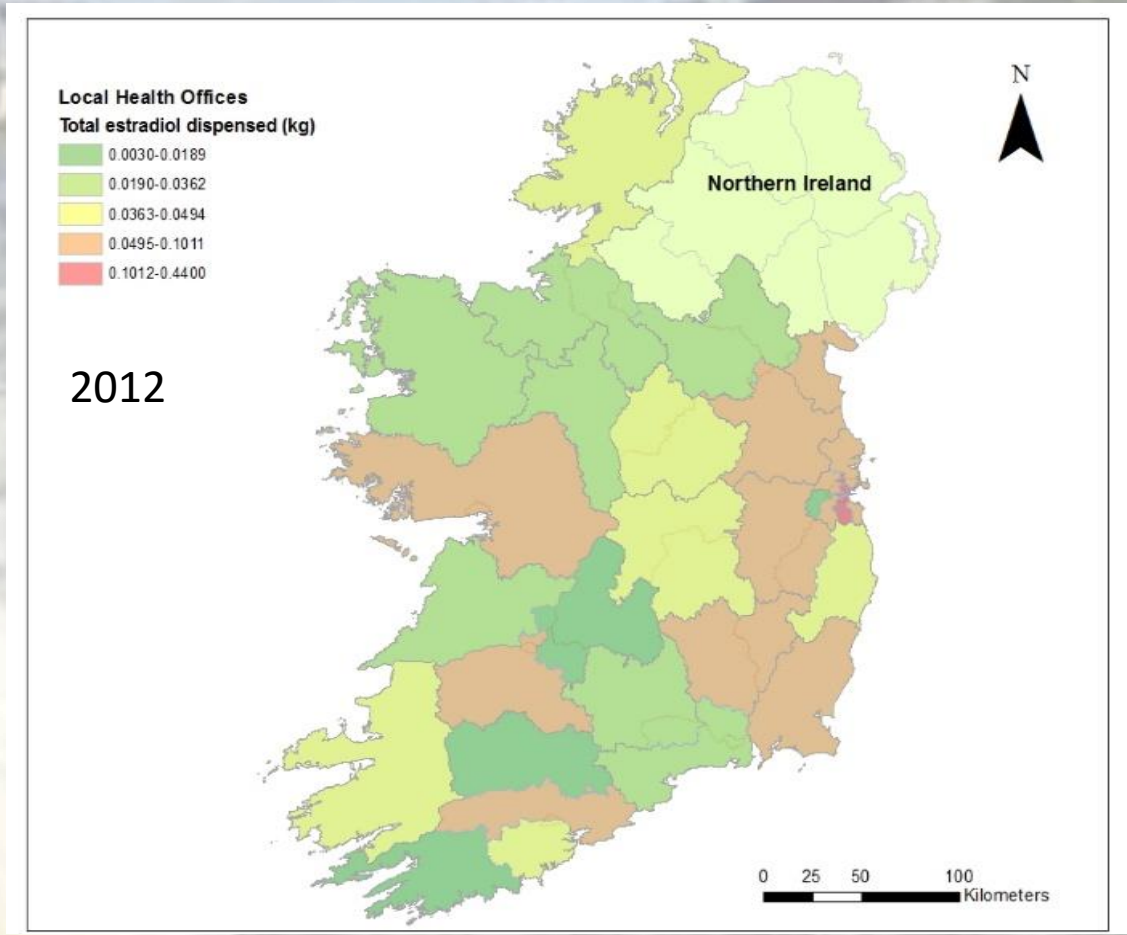
Hayes, J., Kirf, D., Garvey, M., Rowan, N. (2013). Disinfection and toxicological assessments of pulsed-plasma gas-discharge and pulsed UV light treated water containing the waterborne enteroparasite *Cryptosporidium parvum*. *Journal of Microbiological Methods* (94); 325-337.

Barrett, M., Fitzhenry, K., O'Flaherty, V., Dore, W., Rowan, N., Clifford, E. (2016). Detection, fate and inactivation of pathogenic norovirus employing settlement and UV treatment in wastewater treatment facilities. *Science of the Total Environment*. [Oct 15; 568:1026-36. doi:10.1016/j.scitotenv.2016.06.067.

Heat map representing the total volume (kg) of EE2 dispensed (not prescription) in each LHO according to HSE records from three reimbursement schemes; the General Medical Services (GMS), the Drug Payment scheme (DP) and the Long Term Illnesses (LTI) scheme

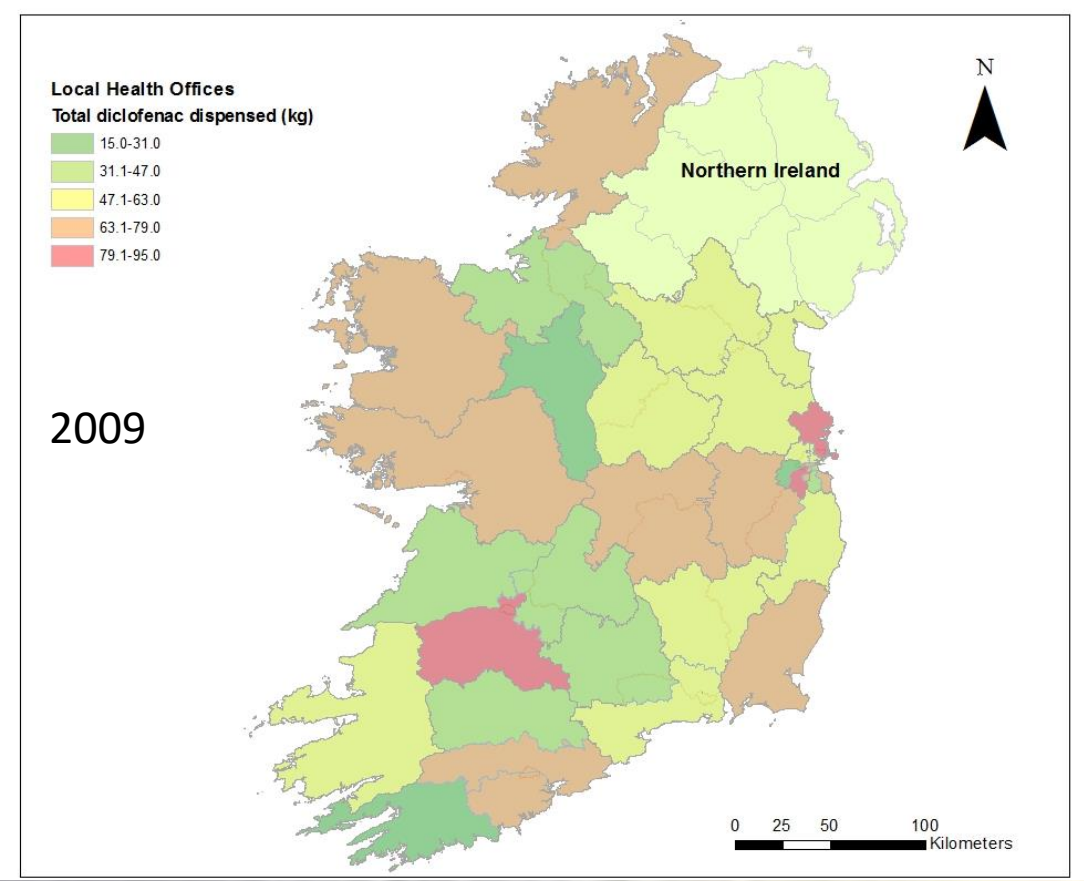


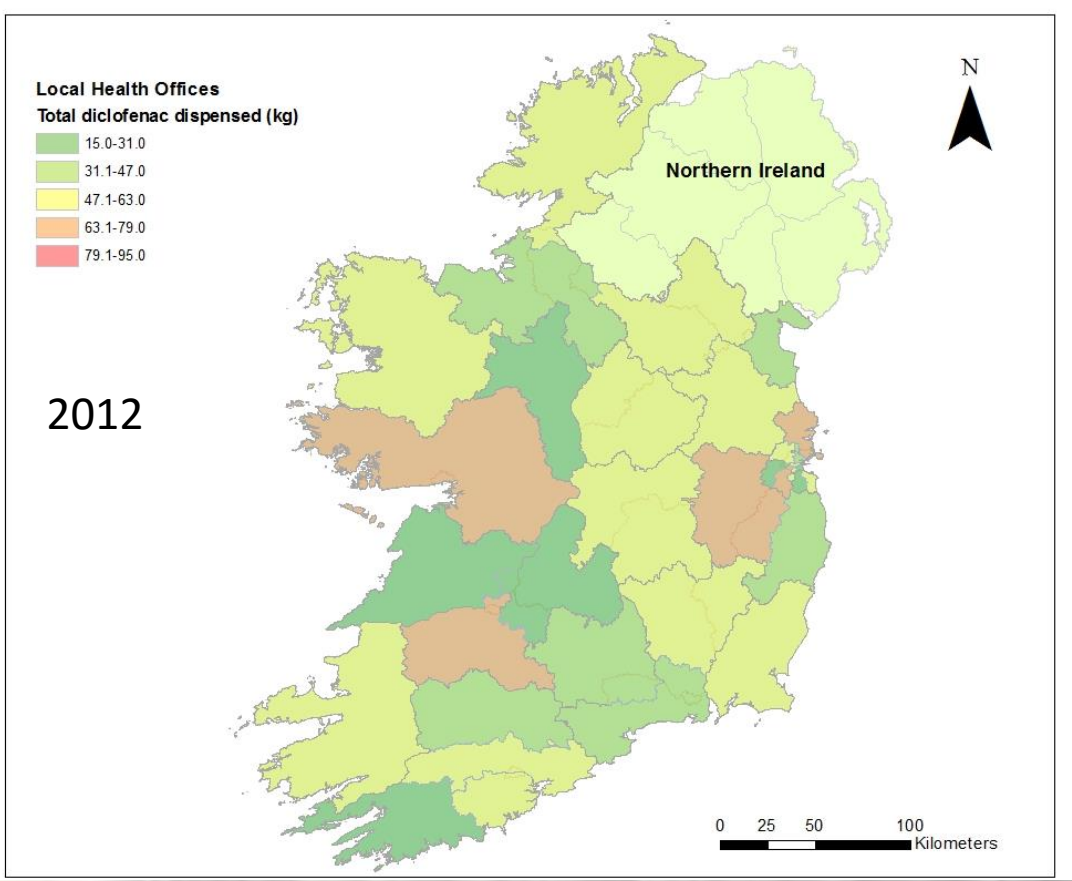
2009



2012

Heat map representing the total volume (kg) of DICLOFENAC dispensed in each LHO, according to HSE records from three reimbursement schemes





GOOD AGREEMENT WITH MONITORED HIGH OCCURRENCES OF DCL AND LHO LOCATIONS OF HIGH DISPENSING DRUG DATA

SEMI-QUANTIATIVE RISK ASSESSMENT MODEL
–
SPECIFIC FOR THREE WATCH LIST PHARMACEUTICAL COMPOUNDS in IRELAND USING WWTPs as CRITICAL CONTROL ASSESSMENT POINTS

RA Model Development

- Model was designed following risk screening guidelines of Section 10, Drinking Water Safety Plans (EPA Handbook on the implementation of the Regulation for Water Service Authorities for Public Supplies (2010)
- Risk Screening Methodology for *Cryptosporidium* was adapted to consider risk factors specific for discharge of PhACs of interest
- General principles of RA model align with EPA-sanctioned risk screen methodology, for example, it uses the **Source-Pathway-Receptor** (SPR) concept to define relevant input parameters
- Scoring system was employed enabling determination of each WWTP as low, medium or high risk
- RA model involves calculating risk score for four main input parameters using data for DCL, E2 and EE2 for 16 WWTPs (varying sizes and distributed evenly) with cumulative (additive) risk designated as low, medium or high

RISK ASSESSMENT (Phase 1)

Risk*:*

Probability of the occurrence of, and magnitude of the consequence of, and unwanted adverse effect on a receptor

Risk Assessment*:*

Process of establishing, to the extent possible, the existence, nature and significance of risk

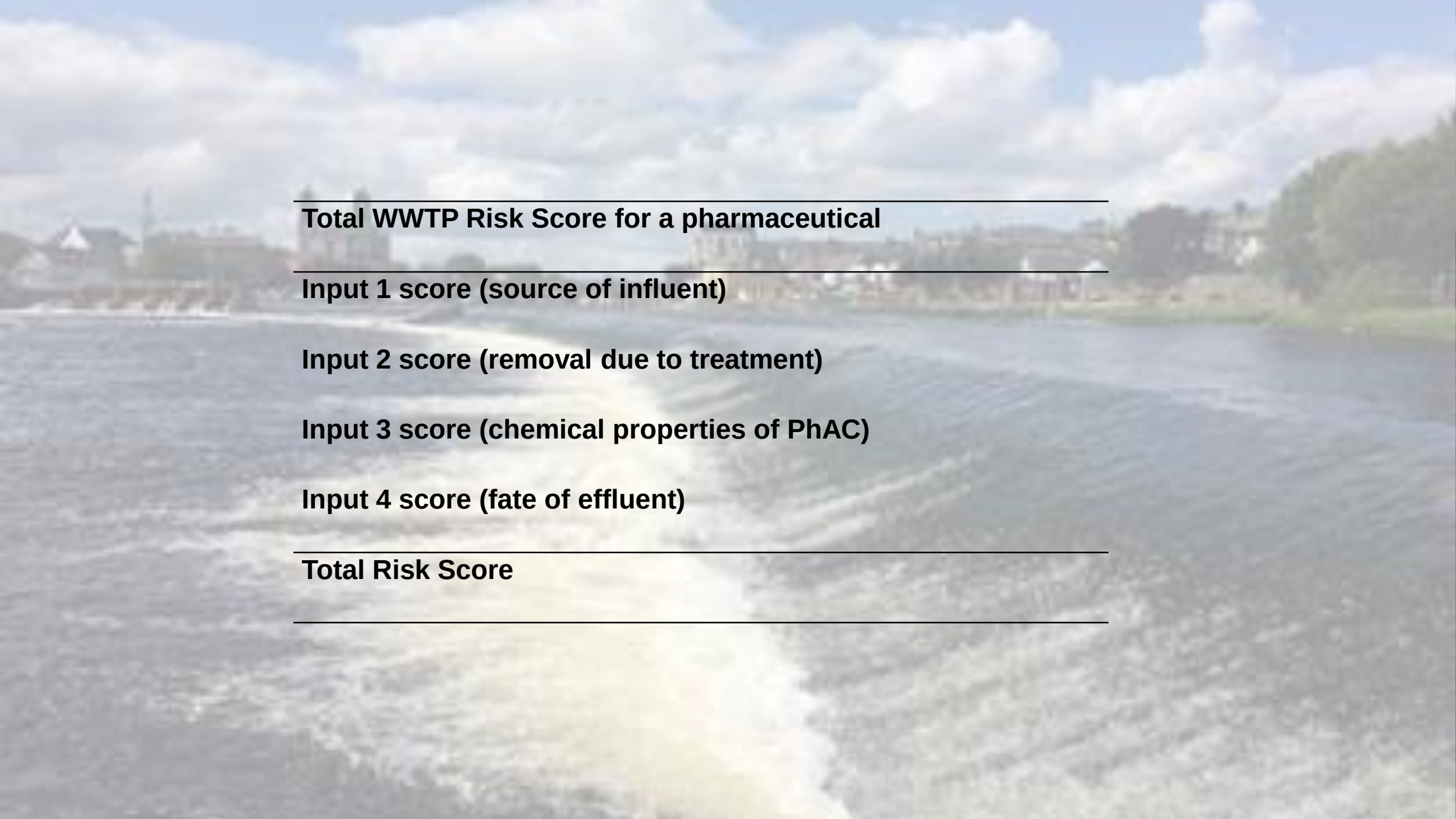
from BS10175; 2001

KEY CONCEPTS to RISK ASSESSMENT

Conceptual Model

Text/schematic hypothesis of the nature and sources of contamination, potential migration pathways (including description of the ground and groundwater) and potential receptors, developed on the basis of information from the phase 1 investigation and defined during subsequent phases of investigation

Source – Pathway - Receptor



Total WWTP Risk Score for a pharmaceutical
Input 1 score (source of influent)
Input 2 score (removal due to treatment)
Input 3 score (chemical properties of PhAC)
Input 4 score (fate of effluent)
Total Risk Score

1 Source of influent factors used in risk assessment model to calculate input one risk score. White indicates factor considered for all 3 compounds, light grey indicates factor considered only for E2 and EE2, dark grey indicates parameter considered only for E2. 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	Source factor description	Risk Score	Actual Score
1- **Agglomeration generated load (AGL)** [size of population serviced by each WWTP – useful indicator of PhAC emissions as organic biodegradable load of a WWTP expressed in population equivalents (PE) – obtained from EPA	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**? {Also considers **hospital effluent**}	No	0	
	Yes	1	
4- **Gender ratio in county, women:men** **[CSO – 2011 Census)**	≤ 1	0	
	> 1	1	
5- **Cattle score (particularly dairy)** [livestock numbers via CSO StatBank online – spatial resolution to regional authority divided by total land area}	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/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			

Missing drug utilisation or prescription data as important factor – yet to be incorporated

2. Removal due to treatment

Factor	Treatment factor description	Risk Score	Actual Score
1- Tertiary treatment (extracted EPA – AERs 2014) = mostly UV	Present year round	-4	
	Implemented seasonally (e,g. bathing season	-2	
	Absent year round	0	
2- Type of secondary treatment (including nutrient removal) (extracted EPA AER 2015}	Extended aeration (N removal) [25.7% of WW load in PE]	-2	
	Sequence batch reactor (with or without P removal)	0	
	Conventional activated sludge (with or without P removal)	0	
3- WWTP quality measurement [BOD, COD, TSS and where applicable, N and P]	Pass most recent UWWTD compliance criteria	0	
	Fail most recent UWWTD compliance criteria	1	
4- Monitoring data [Monitoring DCL, E2, EE2 not legally required, yet for WFD compliance – this relates to independent research data measured at WWTPs in Ireland and findings shown]	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			

Treatment, operation and management factors used in risk assessment model to calculate input two 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)

3. Chemical properties of PhAC

Factor	Chemical properties factor description	Risk Score	Actual Score
1- Metabolism [Rate of excretion, combined with drug usage data, will inform how much drug ends up in wastewater –rates determined from literature for DCL, E2, EE2}	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 to sludge Liklihood correlated to physciochemical parameters: [octanol-water partition coefficient – Kow) or d-octanol-water partition coefficient –Dow; or experimentally determined water-distribution coefficient – Kd value}	Low water solubility/high hydrophobicity, functional group polarity, ion exchange, chelation to other compounds….identified through K_{ow}, D_{ow}, and K_d values, and reports from literature	1	
	High water solubility/low hydrophobicity, functional group polarity, ion exchange, chelation to other compounds…identified through K_{ow}, D_{ow}, and K_d values, and reports from literature	4	
3- Degradation potential	High degradation through photolysis, hydrolysis or other mechanisms, identified through compound half-life in the environment and reports from literature	1	
	Low degradation through photolysis, hydrolysis or other mechanisms, identified through compound half-life in the environment and reports from literature	3	
4-Potenital 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			

missing compound specific or group toxicity unitpicked up via ICRAPHE 2016 presentations

4. Fate of Effluent

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 [Identified in 2001 and 2010 Urban WWT regulations – 2015 EPA AERs]	Primary discharge location not at/near sensitive area	0	
	Primary discharge location at/near sensitive area	1	
3- Flow of receiving water {hydrometric monitoring station closest to WWTP the 95% percentile flow (m3/s) obtained from Water Data Unit of EPA}	High (>10 m3/s)	1	
	Medium (1-10 m3/s)	2	
	Low (<1 m3/s)	3	
Total for Input 4			

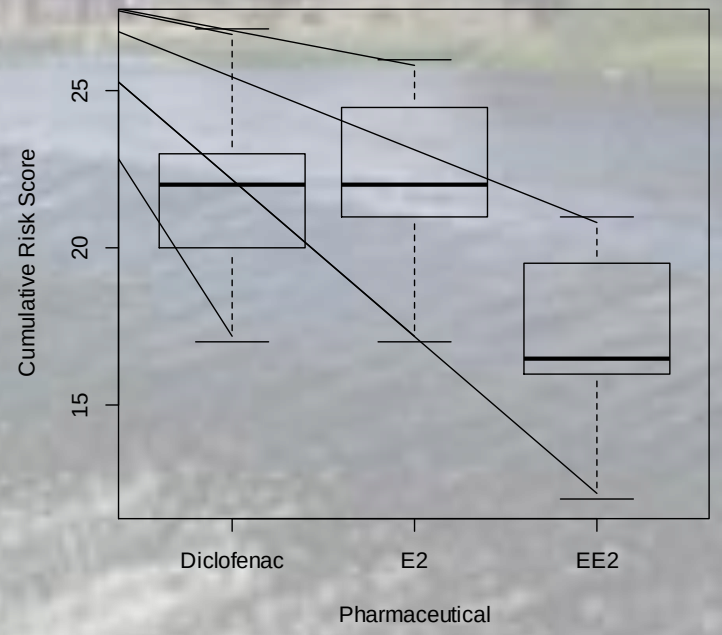
Fate of treated effluent factors used in risk assessment model to calculate input four risk score. The colour of the risk score indicates whether there is increased risk (positive values, red), no impact on risk (zero values, blue) or decreased risk (negative values, green).

Factor scoring for each PhAC of interest for risk assessment model, input three. Final score assigned in model for each factor is in colour and in bold, followed by references used to determine the score

PhAC	Metabolism	Sorption	Degradation	Conjugation
Diclofenac	**3** (Davies & Anderson, 1997) Reviewed in (Vieno & Sillanpää, 2014; Zhang et al, 2008)	**4** (Martín et al, 2012; Patrolecco et al, 2015; Radjenović et al, 2009; Suárez et al, 2012; Ternes et al, 2004) Reviewed in Vieno and Sillanpää (2014)	**3** (Joss et al, 2005; Joss et al, 2006; Quintana et al, 2005) Reviewed in (Vieno & Sillanpää, 2014)	**2** (Clara et al, 2005b; Lacey et al, 2012)
17-beta-estradiol (E2)	**2** (Adlercreutz et al, 1986; D'Ascenzo et al, 2003; de Mes et al, 2005)	**1** (Ben Fredj et al, 2015; Carballa et al, 2008; Ternes, 2006)	**1** (Abargues Llamas et al, 2012b; Alvarino et al, 2014; Petrie et al, 2014; Suárez et al, 2008)	**0** (Johnson et al, 2000)
17-alpha-ethinylestradiol (EE2)	**2** (de Mes et al, 2005; Reed et al, 1972)	**1** (Ben Fredj et al, 2015; Martín et al, 2012; Ternes, 2006)	**2** (Abargues Llamas et al, 2012b; Alvarino et al, 2014; Petrie et al, 2014; Suárez et al, 2008)	**0** (Johnson et al, 2000)

Summary statistics of cumulative (final) risk scores assigned during the case study to the 16 WWTPs included for analysis by the risk assessment model for diclofenac, E2 and EE2.

Summary statistic	Diclofenac	E2	EE2
Maximum	27	26	21
Minimum	17	17	12
Mean	21.94	22.13	17.06
Median	22	22	16.5
Mode	23	21	16
Standard Deviation	2.72	2.85	2.67



DICLOFENAC

WWTP Name	Input 1 (source of influent)	Input 2 (removal during treatment)	Input 3 (chemical properties of compounds)	Input 4 (fate of treated effluent)	Total
Carlow	5	-2	12	5	20
Ballincollig	5	-2	12	4	19
Fermoy	5	0	12	5	22
Ringsend	6	2	12	3	23
Swords	5	1	12	3	21
Galway	6	3	12	2	23
Killarney	6	0	12	5	23
Tralee	6	-4	12	3	17
Leixlip	7	3	12	5	27
Osberstown	7	3	12	5	27
Kilkenny	7	0	12	5	24
Longford	5	0	12	6	23
Tullamore	4	0	12	6	22
Roscommon	3	0	12	6	21
Clonmel	6	-2	12	4	20
Athlone	5	-2	12	4	19

E2

WWTP Name	Input 1 (source of influent)	Input 2 (removal during treatment)	Input 3 (chemical properties of compounds)	Input 4 (fate of treated effluent)	Total
Carlow	12	1	4	5	22
Ballincollig	12	1	4	4	21
Fermoy	12	3	4	5	24
Ringsend	13	1	4	3	21
Swords	12	-2	4	3	17
Galway	11	0	4	2	17
Killarney	13	3	4	5	25
Tralee	13	-1	4	3	19
Leixlip	14	3	4	5	26
Osberstown	14	2	4	5	25
Kilkenny	14	3	4	5	26
Longford	11	3	4	6	24
Tullamore	10	3	4	6	23
Roscommon	8	3	4	6	21
Clonmel	13	1	4	4	22
Athlone	12	1	4	4	21

EE2

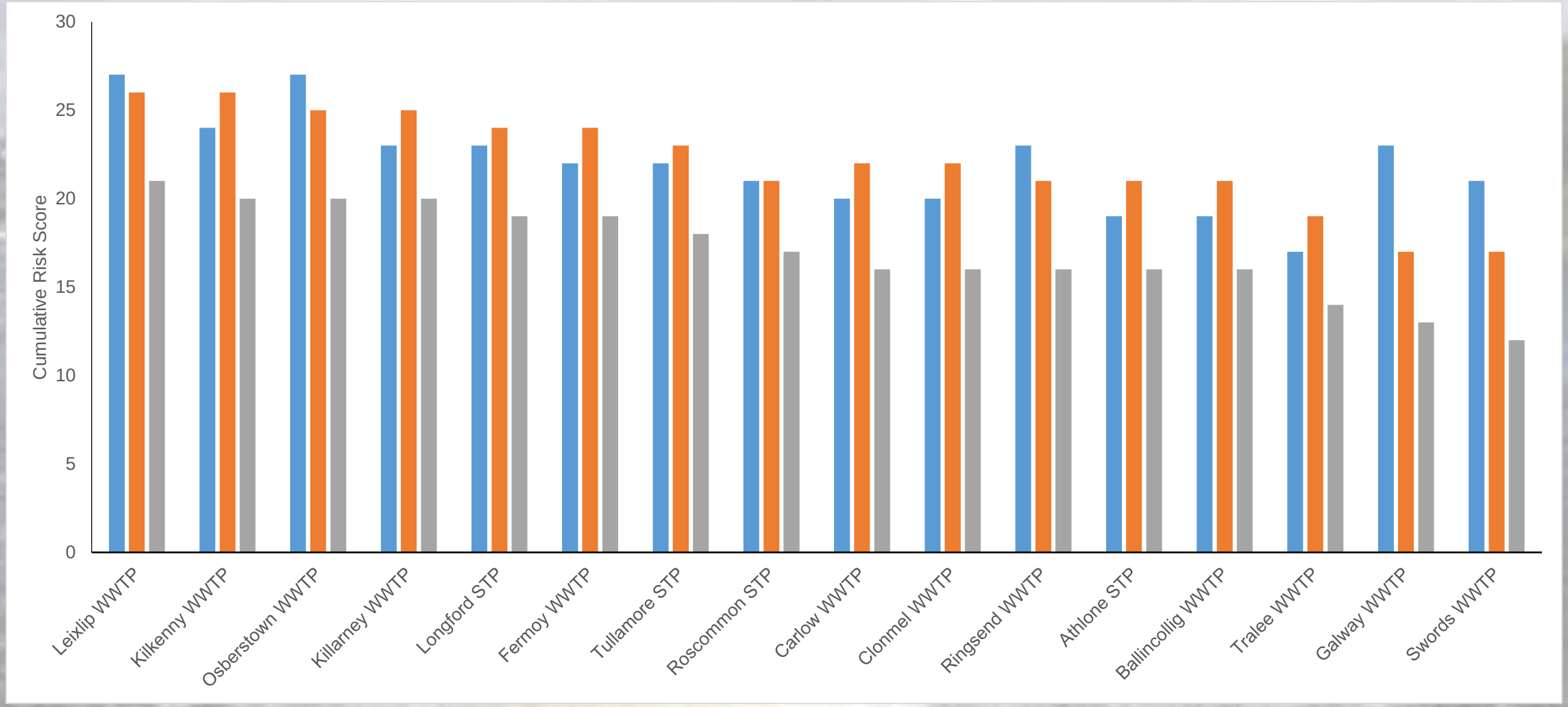
WWTP Name	Input 1 (source of influent)	Input 2 (removal during treatment)	Input 3 (chemical properties of compounds)	Input 4 (fate of treated effluent)	Total
Carlow	5	1	5	5	16
Ballincollig	6	1	5	4	16
Fermoy	6	3	5	5	19
Ringsend	7	1	5	3	16
Swords	6	-2	5	3	12
Galway	6	0	5	2	13
Killarney	7	3	5	5	20
Tralee	7	-1	5	3	14
Leixlip	8	3	5	5	21
Osberstown	8	2	5	5	20
Kilkenny	7	3	5	5	20
Longford	5	3	5	6	19
Tullamore	4	3	5	6	18
Roscommon	3	3	5	6	17
Clonmel	6	1	5	4	16
Athlone	6	1	5	4	16

Results of case study evaluating 16 Irish WWTP using the developed risk assessment model for diclofenac, E2 and EE2

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

WWTPS are ranked for each PhAC from highest-lowest risk, based on the cumulative (total) risk scores assigned by the model. A colour change indicates a decrease in the cumulative risk score (red = higher risk → green = lower risk), and WWTPs that share the same colour had the same final score, and thus are ranked equally.

Cumulative (total) risk scores for each of the 16 WWTPs included in the case study, assigned via the risk assessment model for diclofenac (blue bars), E2 (red bars) and EE2 (green bars).



Recommendations/Policy Implications for Ireland

- **Advocate for 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**
  - **Given positive results and outcomes from studies that utilise effect-based (biological) monitoring, passing sampling or an integrated monitoring approaches, advocate the acceptance of these types of methodologies for substance reporting.**
- **Continue funding Irish projects on emerging/established pollutants (short-term, EPA)**
  - **EPA-funded research is currently the only significant source of aquatic monitoring data for watch-list substances in Ireland to expand for other substances/groups of substances in aquatic and other environmental matrices (sludge, sediment, biota)**
- **Develop and extend the semi-quantitative RA model created during this project (short term, EPA)**
  - **Additional model development needed to augment predictive ability and robustness, and to increase significance and accuracy of its conclusions**
  - **Consider alignment with other European RA models for future development**
  - **Future studies to include a combination of field-based monitoring of PhAC concentrations in influent, effluent and receiving waters (for model validation)**

Recommendations/Policy Implications for Ireland

- **Identify sources and improve availability of PhAC data (short term, EPA)**
  - **Project identified sources of national PhAC (usage) consumption data quickly, but experienced delays with data acquisition**
  - **More data should be collected on prescriptions written and dispensed by public and private health agencies in Ireland**
  - **Such data should be made available to researchers in Ireland**
  - **Find means to hurdle the unavailability of commercially-sensitive data such as PhAC sales/production information**
- **Consider more than just the parent compound (short term, future research)**
  - **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**

Recommendations/Policy Implications for Ireland

- **Institute change 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 they produce**
  - **We recommend changes to policy be considered, both nationally and internationally.**
  - **Before a product is approved for market, some toxicity testing is typically required, but there is a scenario or mechanism in which the human benefits that come form consumption of PhAC could be outweighed by negative environmental impacts**
  - **At 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 substance to market**
  - **In long term, it may be advisable for Ras of PhACs to include environmental risk and persistence and not just the risk to the consumer of the product**

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