CREW CENTRE OF EXPERTISE FOR WATERS

Pharmaceuticals in the water environment: baseline assessment and recommendations

Appendices

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Hydro Nation International Centre

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CREW CENTRE OF EXPERTISE FOR WATERS

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Appendix I List of 25 pharmaceuticals identified as Environmentally Harmful by the Stockholm group (in Swedish)

Förteckning över miljöbelastande läkemedel med åtgärdsförslag framtagen inom ramen för Region Stockholms miljöprogram 2017–2021		
Substans	**Motiveringar** **Mätningar avser Sverige om inget annat anges.**	**Åtgärdsförslag** **Åtgärdsförslagen är framtagna i samråd med Region Stockholms läkemedelskommitté och dess expertgrupper, och är utifrån ett miljöperspektiv för att uppnå målet i miljöprogrammet med minskade utsläpp av miljöbelastande läkemedel. Observera att patientens bästa alltid går i första hand, se rekommenderade läkemedel i Kloka listan. Flera läkemedel på förteckningen finns också med i Kloka listan men även för sådana läkemedel finns konkreta tips på hur man kan arbeta som kan innebära minskad belastning på miljön. För flera miljöbelastande substanser har miljöutredningar genomförts för jämförbara alternativ på Kloka listan.**
Amoxicillin	På grund av risk för ekotoxiska halter av amoxicillin i vatten övervakas substansen inom ramen för EU:s vattenlagstiftning för att "öka kunskapen om förekomst och spridning av antimikrobiella substanser i miljön". Utifrån förväntade koncentrationer i avloppsreningsverk riskerar amoxicillin att selektera för antibiotikaresistenta bakterier.	• Amoxicillin rekommenderas i Kloka listan. Eradikering av Helicobacter pylori endast på strikt indikation. • För antibiotika gäller generellt så restriktiv användning som möjligt utan att riskera patientens hälsa. Relevanta odlingar viktigt för att kunna välja antibiotikum som har god effekt med så smalt spektrum som möjligt.
Azitromycin	På grund av risk för ekotoxiska halter av azitromycin i vatten övervakas substansen inom ramen för EU:s vattenlagstiftning. Utifrån uppmätta halter i avloppsreningsverk selekterar azitromycin eventuellt för antibiotikaresistenta bakterier. Kan "samverka" i miljön med övriga makrolidantibiotika, exempelvis erytromycin, klaritromycin och roxitromycin.	• Azitromycin rekommenderas i Kloka listan för behandling av Mycoplasma genitalium. • För antibiotika gäller generellt så restriktiv användning som möjligt utan att riskera patientens hälsa. Relevanta odlingar viktigt för att kunna välja antibiotikum som har god effekt med så smalt spektrum som möjligt.
Ciprofloxacin	På grund av risk för ekotoxiska halter av ciprofloxacin i vatten övervakas substansen inom ramen för EU:s vattenlagstiftning för att "öka kunskapen om förekomst och spridning av antimikrobiella substanser i miljön". Utifrån uppmätta halter i avloppsreningsverk riskerar ciprofloxacin att selektera för antibiotikaresistenta bakterier.	• Ciprofloxacin rekommenderas vid febril UVI hos vuxna i Kloka listan som alternativ förstahandsbehandling tillsammans med trimetoprim-sulfametoxazol. • Ciprofloxacin ska inte användas vid empirisk behandling av nedre urinvägsinfektion utan feber, då rekommenderas nitrofurantoin (i Kloka listan och är bättre från miljösynpunkt än ciprofloxacin) eller pivmecillinam (i Kloka listan och är ett rimligt alternativ till ciprofloxacin från miljösynpunkt). Nitrofurantoin bedöms utgöra den lägsta miljörisken av dessa. • För antibiotika gäller generellt så restriktiv användning som möjligt utan att riskera patientens hälsa. Relevanta odlingar viktigt för att kunna välja antibiotikum som har god effekt med så smalt spektrum som möjligt.

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Citalopram, escitalopram	Koncentrationer av citalopram i fisk exponerad för renat avloppsvatten motsvarar terapeutiska nivåer hos människa. Halter i miljön av flera SSRI/SNRI överstiger de koncentrationer som rapporterats ha påverkan på vattenlevande organismer, särskilt ryggradslösa djur.	• Vid behandling av depression sätts i första hand icke farmakologisk behandling och/eller åtgärder in (t.ex. KBT och fysisk aktivitet) ensamt eller i kombination med läkemedel. Undvik överkonsumtion av alkohol. • Citalopram rekommenderas inte i Kloka listan. Istället rekommenderas escitalopram. Från miljösynpunkt finns det en riskbild för såväl rekommenderade läkemedel i Kloka listan (escitalopram, fluoxetin, klomipramin och sertralin) som för sådana som inte rekommenderas (paroxetin och venlafaxin). För substanser där det finns god information om miljörisken innebär det ingen uppenbar förbättring att byta ut en substans mot en annan. För övriga substanser är osäkerheten kring miljörisken för stor för att byte ska kunna rekommenderas från miljösynpunkt. • Undvik slentrianmässig förskrivning av SSRI-preparat (exempelvis escitalopram/citalopram). Utvärdera och ompröva behandlingen med SSRI-preparat. Kan läkemedlet sättas ut? • Startförpackning för escitalopram finns inom förmånen.
Diazepam	Halter av diazepam i vattendrag är låga och bedöms ej medföra någon risk. Diazepam metaboliseras dock till viss del till oxazepam som i sin tur finns i halter som medför risk för miljöpåverkan. Därför kan användning av diazepam bidra till risken.	• Diazepam, rektalt och intravenöst, rekommenderas vid epilepsi och status migränosus i Kloka listan. • Långverkande bensodiazepiner, exempelvis diazepam tabletter, bör undvikas till äldre.
Diklofenak	På grund av risk för ekotoxiska halter i vatten har diklofenak tidigare övervakats inom ramen för EU:s vattenlagstiftning. Nu finns tillräckligt med data för att bedöma om diklofenak ska föreslås som ett prioriterat ämne när EU-kommissionen nästa gång föreslår ett reviderat så kallat prioämnesdirektiv. För Sveriges del har Havs- och vattenmyndigheten med diklofenak bland särskilda förorenande ämnen (SFÄ) i sin föreskrift HVMFS 2013:19 (Uppdaterad 2017-01-01), Diklofenak återfinns i ytvatten i halter som rapporterats ha effekter på fisk	• Diklofenak rekommenderas inte i Kloka listan. De NSAID-preparat (ibuprofen, ketoprofen och naproxen) + paracetamol som rekommenderas i Kloka listan är alla bättre från miljösynpunkt än diklofenak. Paracetamol är ett mycket säkert alternativ från miljösynpunkt. Även övriga bedöms medföra en låg miljörisk, något förhöjd för ketoprofen. • Observera att diklofenak även säljs receptfritt (tabletter, gel, plåster och spray). På grund av risker för hjärtkärlbiverkningar beslutade Läkemedelsverket att receptbelägga tabletter och kapslar med diklofenak från den 1 juni 2020. Utvärtes beredningar med diklofenak berörs inte av beslutet och säljs fortsatt receptfritt. Hur ser era rekommendationer ut till patienter vad gäller receptfria smärtlindrande läkemedel?
Erytromycin	På grund av risk för ekotoxiska halter av erytromycin i vatten övervakas substansen inom ramen för EU:s vattenlagstiftning. Utifrån uppmätta halter i avloppsreningsverk riskerar erytromycin att selektera för antibiotikaresistenta bakterier. Kan "samverka" i miljön med övriga makrolidantibiotika, exempelvis azitromycin, klaritromycin och roxitromycin.	• Erytromycin rekommenderas i Kloka listan. • För antibiotika gäller generellt så restriktiv användning som möjligt utan att riskera patientens hälsa. Relevanta odlingar viktigt för att kunna välja antibiotikum som har god effekt med så smalt spektrum som möjligt.

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Estradiol	På grund av risk för ekotoxiska halter av estradiol i vatten övervakas substansen inom ramen för EU:s vattenlagstiftning. Bidrar till östrogenhalter i miljön tillsammans med exempelvis etinylestradiol och kroppseget östrogen. Se vidare etinylestradiol.	• Estradiol rekommenderas i Kloka listan. • Individuell anpassning av preventivmedel såväl som läkemedel för behandling av klimakteriebesvär och symtomgivande vaginal atrofi är viktigt för att optimera behandlingen och undvika biverkningar. • Vid lokal applicering av plåster med estradiol (Estradot, rekommenderas i Kloka listan) mot klimakteriebesvär är den mängd läkemedel som tillförs en individ avsevärt lägre än den dos som krävs för att ge motsvarande effekt med estradioltabletter. • Säkerställ att ni inom den egna verksamheten kasserar överblivet läkemedel samt brukade plåster och vaginalinlägg på ett korrekt sätt, http://www.janusinfo.se/Rutiner/Hantering-av-lakemedel/. • Informera patienten om vikten av att kassera överblivet läkemedel samt brukade plåster och vaginalinlägg på ett korrekt sätt (patientfolder "Skydda miljön släng rätt").
Etinylestradiol	På grund av risk för ekotoxiska halter av etinylestradiol i vatten övervakas substansen inom ramen för EU:s vattenlagstiftning. Halter i vatten bedöms i vissa fall vara tillräckligt höga för att kunna påverka fortplantning och könsutveckling hos fisk.	• Etinylestradiol (kombinerade preventivmedel) rekommenderas i Kloka listan. • Individuell anpassning av preventivmedel är viktigt för att optimera behandlingen och undvika biverkningar. • Säkerställ att ni inom den egna verksamheten kasserar överblivet läkemedel samt brukade p-ringar och plåster på ett korrekt sätt, http://www.janusinfo.se/Rutiner/Hantering-av-lakemedel/. • Informera patienten om vikten av att kassera överblivet läkemedel samt brukade p-ringar och plåster på ett korrekt sätt (patientfolder "Skydda miljön släng rätt").
Felodipin	Halter i miljön bedöms kunna leda till terapeutiska nivåer i fisk baserat på ämnets fettlöslighet.	• Felodipin rekommenderas inte i Kloka listan. I stället rekommenderas amlodipin som är bättre från miljösynpunkt än felodipin.
Fluoxetin	Fluoxetin har uppmätts i vild fisk, dock i sådana koncentrationer som motsvarar subterapeutiska nivåer hos människa. Halter i miljön av flera SSRI/ SNRI överstiger de som rapporterats ha påverkan på vattenlevande organismer, särskilt ryggradslösa djur.	• Vid behandling av depression sätts i första hand icke farmakologisk behandling och/eller åtgärder in (t.ex. KBT och fysisk aktivitet) ensamt eller i kombination med läkemedel. Undvik överkonsumtion av alkohol. • Fluoxetin rekommenderas i Kloka listan i första hand till barn och ungdomar vid depression. Fluoxetin rekommenderas i Kloka listan i andra hand vid ångestsyndrom respektive tvångssyndrom och relaterade tillstånd. Från miljösynpunkt finns det en riskbild för såväl rekommenderade läkemedel i Kloka listan (escitalopram, fluoxetin, klomipramin och sertralin) som för sådana som inte rekommenderas (paroxetin och venlafaxin). För substanser där det finns god information om miljörisken innebär det ingen uppenbar förbättring att byta ut en substans mot en annan. För övriga substanser är osäkerheten kring miljörisken för stor för att byte ska kunna rekommenderas från miljösynpunkt. • Undvik slentrianmässig förskrivning av SSRI-preparat (exempelvis fluoxetin). Utvärdera och ompröva behandlingen med SSRI-preparat. Kan läkemedlet sättas ut? • Startförpackning finns inom förmånen.

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Flupentixol	Utifrån uppmätta halter i ytvatten beräknas flupentixol kunna ansamlas i fisk till terapeutiska koncentrationer.	• Flupentixol rekommenderas inte i Kloka listan. • Ett alternativ vid nyinsättning kan vara aripiprazol (rekommenderas i Kloka listan och är bättre från miljösynpunkt än flupentixol).
Glibenklamid	Glibenklamid har uppmätts i vild fisk i sådana koncentrationer som är nära terapeutiska nivåer hos människa. Det stöds av ämnets fettlöslighet och uppmätta koncentrationer i avloppsvatten.	• Glibenklamid rekommenderas inte i Kloka listan. • Individuell anpassning av läkemedel vid behandling av diabetes mellitus typ 2 är viktigt för att optimera behandlingen och undvika biverkningar. • Alternativ kan vara glimepirid (rekommenderas i Kloka listan och har ungefär samma miljörisk som glibenklamid) eller repaglinid (rekommenderas i Kloka listan och är bättre från miljösynpunkt än glibenklamid). • Hälsosamma levnadsvanor som viktnedgång vid övervikt, ökad fysisk aktivitet, väl sammansatt kost och att undvika överkonsumtion av alkohol skulle kunna bidra till minskad läkemedelsanvändning hos vissa patienter.
Haloperidol	Haloperidol har uppmätts i vild fisk och fisk exponerad för renat avloppsvatten i nivåer nära terapeutiska koncentrationer hos människa. Det stöds av ämnets fettlöslighet och uppmätta koncentrationer i ytvatten.	• Haloperidol rekommenderas inte i Kloka listan. • Ett alternativ vid nyinsättning till patienter med schizofreni kan vara aripiprazol (rekommenderas i Kloka listan och är bättre från miljösynpunkt än haloperidol).
Irbesartan	Utifrån uppmätta halter i ytvatten beräknas irbesartan kunna ansamlas i fisk till terapeutiska koncentrationer. Uppmätta koncentrationer i enstaka studerade fiskar har dock varit lägre.	• Irbesartan rekommenderas inte i Kloka listan. • Alternativ som angiotensinreceptorblockerare kan vara kandesartan (rekommenderas i Kloka listan men osäkert bedömningsunderlag gör att det inte går att avgöra om det är fördelaktigt ur ett miljöperspektiv) eller losartan (rekommenderas i Kloka listan och är bättre från miljösynpunkt än irbesartan). • Startförpackningar för kandesartan och losartan finns inom förmånen.
Klaritromycin	På grund av risk för ekotoxiska halter av klaritromycin i vatten övervakas substansen inom ramen för EU:s vattenlagstiftning. Utifrån uppmätta halter i avloppsreningsverk riskerar klaritromycin att selektera för antibiotikaresistenta bakterier. Kan "samverka" i miljön med övriga makrolidantibiotika, exempelvis azitromycin, erytromycin och roxitromycin.	• Klaritromycin rekommenderas i Kloka listan. Eradikering av Helicobacter pylori endast på strikt indikation. • För antibiotika gäller generellt så restriktiv användning som möjligt utan att riskera patientens hälsa. Relevanta odlingar viktigt för att kunna välja antibiotikum som har god effekt med så smalt spektrum som möjligt.

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Levonorgestrel	Beräknade halter i ytvatten kan vara tillräckliga för att störa fortplantning i fisk. Fisk exponerad för renat avloppsvatten ansamlar läkemedlet till koncentrationer som överskrider terapeutiska koncentrationer hos kvinnor som tar p-piller.	• Levonorgestrel rekommenderas i Kloka listan. • Individuell anpassning av preventivmedel är viktigt för att optimera behandlingen och undvika biverkningar. • Vid användning av perorala kombinerade hormonella preventivmedel är den mängd levonorgestrel som tillförs per dygn flerfalt högre än den dos som avges med de långverkande levonorgestrel-avgivande hormonspiralerna. Jaydess, Levosert och Kyleena (rekommenderas i Kloka listan) kan därför från miljösynpunk vara alternativ till kombinerade p-piller. Den långverkande p-staven Nexplanon med etonogestrel är ett annat alternativ (rekommenderas i Kloka listan). • Säkerställ att ni inom den egna verksamheten kasserar överblivet läkemedel samt brukade hormonspiraler och p-stavar på ett korrekt sätt. • Informera patienten om vikten av att kassera överblivet läkemedel på ett korrekt sätt (patientfoldern "Skydda miljön släng rätt").
Meklozin	Utifrån uppmätta halter beräknas meklozin kunna ansamlas i fisk till terapeutiska koncentrationer. Meklozin har dock i dagsläget inte hittats i fisk.	• Meklozin (Postafen) rekommenderas i Kloka listan. • Receptfri förpackning om 10 tabletter finns utan förmån. Denna förpackning rekommenderas när så är möjligt. Därutöver finns förpackning om 100 tabletter inom förmånen.
Oxazepam	Har uppmätts i miljön i halter mycket nära de koncentrationer som påverkar beteendet hos fisk. Uppmätt i vild fisk i halter som kan kopplas till stört beteendemönster.	• Tillfälliga orostillstånd behöver inte behandlas farmakologiskt. • Oxazepam rekommenderas som tillfällig symtomlindring vid ångestbesvär hos äldre och som abstinensbehandling vid alkoholsjukdomar i Kloka listan. • Bensodiazepiner kan försämra kognition samt öka risken för fall och därmed frakturer hos äldre. Endast oxazepam i lägsta effektiva dos och under kort tid (högst 2 veckor) kan rekommenderas till äldre. Alla bensodiazepiner bör dock undvikas i möjligaste mån. • Lugnande medel ska endast användas för korttidsbehandling. • Små förpackningar finns inom förmånen.
Risperidon	Uppmätta halter i vild fisk motsvarar terapeutiska koncentrationer hos människa, vilket stöds av ämnets fettlöslighet och uppmätta halter i avloppsvatten.	• Risperidon rekommenderas i Kloka listan. • Ett alternativ vid nyinsättning till patienter med schizofreni kan vara aripiprazol (rekommenderas i Kloka listan och är bättre från miljösynpunkt än risperidon). • Endast rekommenderat som korttidsbehandling vid psykotiska symtom eller svår aggression till äldre. • Startförpackning finns inom förmånen för vissa styrkor.
Roxitromycin	Utifrån uppmätta halter i avloppsreningsverk selekterar roxitromycin eventuellt för antibiotikaresistenta bakterier. Kan "samverka" i miljön med övriga makrolidantibiotika, exempelvis azitromycin, erytromycin och klaritromycin.	• Roxitromycin rekommenderas inte i Kloka listan. • För antibiotika gäller generellt så restriktiv användning som möjligt utan att riskera patientens hälsa. Relevanta odlingar viktigt för att kunna välja antibiotikum som har god effekt med så smalt spektrum som möjligt.

Substans	Motiveringar	Åtgärdsförslag
	Mätningar avser Sverige om inget annat anges.	**Åtgärdsförslagen är framtagna i samråd med Region Stockholms läkemedelskommitté och dess expertgrupper, och är utifrån ett miljöperspektiv för att uppnå målet i miljöprogrammet med minskade utsläpp av miljöbelastande läkemedel. Observera att patientens bästa alltid går i första hand, se rekommenderade läkemedel i Kloka listan. Flera läkemedel på förteckningen finns också med i Kloka listan men även för sådana läkemedel finns konkreta tips på hur man kan arbeta som kan innebära minskad belastning på miljön. För flera miljöbelastande substanser har miljöutredningar genomförts för jämförbara alternativ på Kloka listan.**
Sertralin	Sertralin har hittats i vild fisk i koncentrationer nära terapeutiska nivåer hos människa. Halter i miljön av flera SSRI/SNRI överstiger de koncentrationer som rapporterats ha påverkan på vattenlevande organismer, särskilt ryggradslösa djur.	• Vid behandling av depression sätts i första hand icke farmakologisk behandling och/eller åtgärder in (t.ex. KBT och fysisk aktivitet) ensamt eller i kombination med läkemedel. Undvik överkonsumtion av alkohol. • Sertralin rekommenderas i Kloka listan. Från miljösynpunkt finns det en riskbild för såväl rekommenderade läkemedel i Kloka listan (escitalopram, fluoxetin, klomipramin och sertralin) som för sådana som inte rekommenderas (paroxetin och venlafaxin). För substanser där det finns god information om miljörisken innebär det ingen uppenbar förbättring att byta ut en substans mot en annan. För övriga substanser är osäkerheten kring miljörisken för stor för att byte ska kunna rekommenderas från miljösynpunkt. • Undvik slentrianmässig förskrivning av SSRI-preparat (till exempel sertralin). Utvärdera och ompröva behandlingen med SSRI-preparat. Kan läkemedlet sättas ut? • Startförpackning finns inom förmånen.
Tetracyklin	Utifrån uppmätta halter i avloppsreningsverk riskerar tetracyklin att selektera för antibiotikaresistenta bakterier.	• Tetracyklin rekommenderas inte i Kloka listan. Observera att lymecyklin, som rekommenderas i Kloka listan, snabbt hydrolyseras till aktivt tetracyklin i samband med absorption. Lymecyklin rekommenderas i andra hand vid medelsvår till svår papulopustulös akne respektive i andra hand vid medelsvår till svår rosacea. • För antibiotika gäller generellt så restriktiv användning som möjligt utan att riskera patientens hälsa. Relevanta odlingar viktigt för att kunna välja antibiotikum som har god effekt med så smalt spektrum som möjligt.
Trimetoprim	Utifrån uppmätta halter i avloppsreningsverk riskerar trimetoprim att selektera för antibiotikaresistenta bakterier.	• Trimetoprim rekommenderas i Kloka listan efter urinodling om bakterien är känslig. • Vid empirisk behandling av nedre urinvägsinfektion utan feber rekommenderas i Kloka listan nitrofurantoin, som är bättre från miljösynpunkt än trimetoprim, eller pivmecillinam, som utifrån risken för selektion av resistens i reningsverk förefaller vara ett något bättre alternativ än trimetoprim. Växelbruk på individnivå rekommenderas för att minska risken för resistensutveckling. • För antibiotika gäller generellt så restriktiv användning som möjligt utan att riskera patientens hälsa. Relevanta odlingar viktigt för att kunna välja antibiotikum som har god effekt med så smalt spektrum som möjligt.
Venlafaxin	Venlafaxin har hittats i fisk exponerad för renat avloppsvatten, dock i halter under terapeutiska nivåer hos människa. Halter i miljön av flera SSRI/ SNRI överstiger de koncentrationer som rapporterats ha påverkan på vattenlevande organismer, särskilt ryggradslösa djur.	• Vid behandling av depression sätts i första hand icke farmakologisk behandling och/eller åtgärder in (t.ex. KBT och fysisk aktivitet) ensamt eller i kombination med läkemedel. Undvik överkonsumtion av alkohol. • Venlafaxin rekommenderas inte i Kloka listan. Från miljösynpunkt finns det en riskbild för såväl rekommenderade läkemedel i Kloka listan (escitalopram, fluoxetin, klomipramin och sertralin) som för sådana som inte rekommenderas (paroxetin och venlafaxin). För substanser där det finns god information om miljörisken innebär det ingen uppenbar förbättring att byta ut en substans mot en annan. För övriga substanser är osäkerheten kring miljörisken för stor för att byte ska kunna rekommenderas från miljösynpunkt. • Startförpackning finns inom förmånen.

Appendix II List of substances in the project database

Substance	Therapeutic Group	Number of datapoints
10,11-Dihydroxycarbazepine or 10,11- Dihydroxycarbamazepine	Human metabolite - anticonvulsant	3
10,11-Epoxy-carbamazepine	Human metabolite - anticonvulsant	83
17-Alpha ethinyloestradiol (EE2)	Estrogen hormone	134
17-Beta oestradiol (E2)	Estrogen hormone	122
4-Hydroxydiclofenac	Human metabolite – NSAID	8
Amitriptyline	Antidepressant	3
Amphetamine	Stimulant	9
Atenolol	Antihypertensive	113
Atorvastatin	Statin	80
Azithromycin	Antibiotic	86
Benzoylecgonine	Human metabolite – stimulant	28
Bezafibrate	Lipid lowering	27
Caffeine	Stimulant	30
Carbamazepine	Anticonvulsant	145
Chlorpheniramine	Antihistamine	1
Ciprofloxacin	Antibiotic	110
Citalopram	Antidepressant	32
Clarithromycin	Clarithromycin	153
Clopidogrel	Blood thinner	5
Cocaine	Stimulant	1
Cotinine	Stimulant and metabolite	4
Cyclophosphamide	Cytostatic	16
Diazepam	Anxiolytic	2
Diclofenac	NSAID	174
Erythromycin	Antibiotic	146
Estriol (E3)	Estrogen hormone	10
Fluoxetine	Antidepressant	109
Gabapentin	Anticonvulsant	5
Gliclazide	Sulfonylurea	1
Ibuprofen	NSAID	144
Ifosfamide	Cytostatic	16
Iohexol	Contrast agent	19
Irbesartan	Antihypertensive	3
Lidocaine	Anaesthetic	29
Lorazepam	Anxiolytic	1
Losartan	Antihypertensive	3
Metformin	Antidiabetic	86

Appendix III Project database (Excel)

(See separate file)

Appendix IV Guide to maps and gap analysis

Guide to maps

A simplification to the maps was made with regard to the NHS and WWTW facilities. Cartography classes in Table V-A1 were used in both the gap analysis map and the risk maps; Table V-A2 only to the risk maps (full detail of the WWTW Type was retained in the gap analysis map).

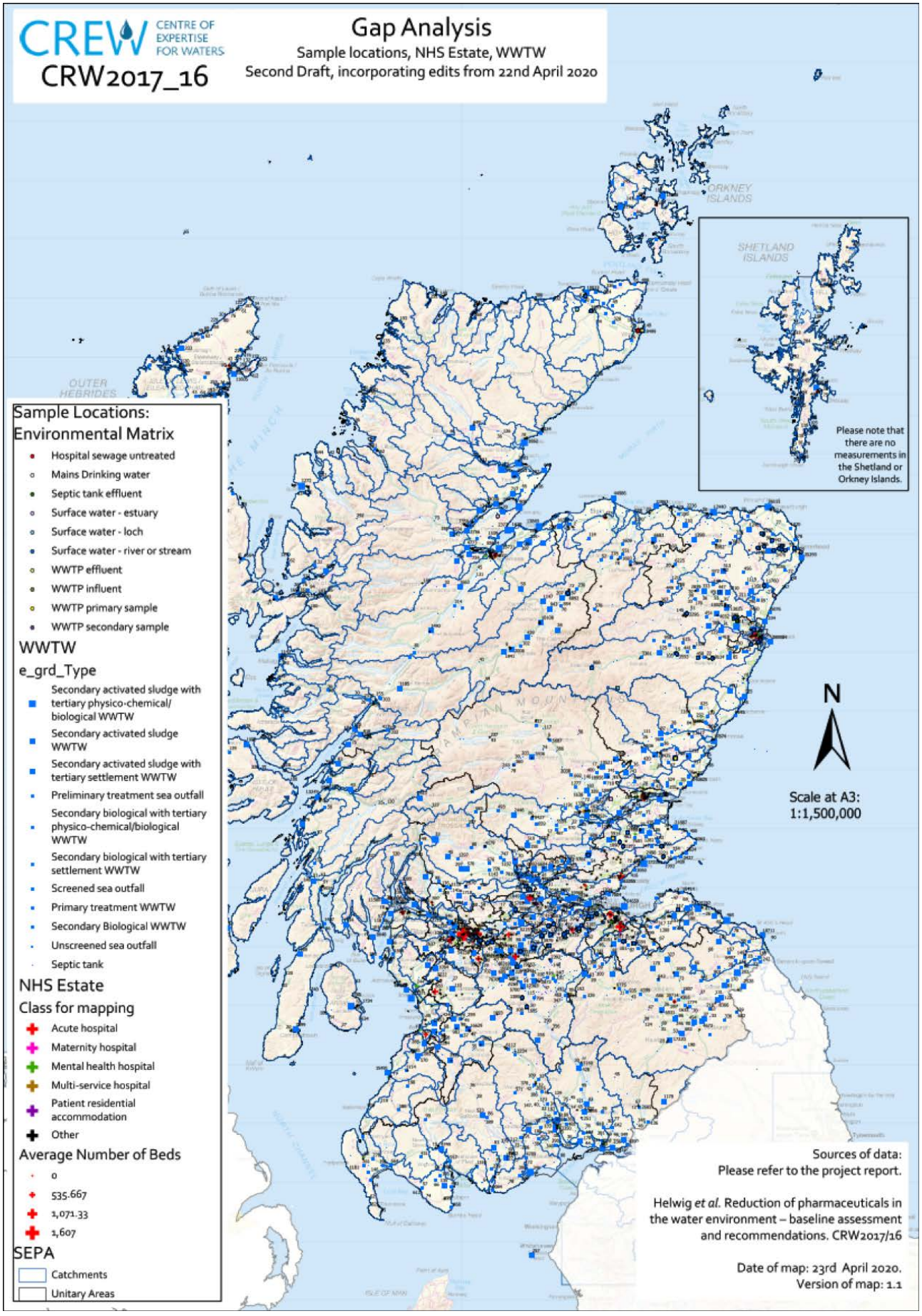
Table V-A1 NHS Site to Cartography class, with frequency

Use	Cartography Class	FREQUENCY
	Other	77
01 Acute Hospital	Acute hospital	30
02 Children's Hospital	Other	3
03 Maternity Hospital	Maternity hospital	2
04 Specialist Hospital	Other	10
05 Mental Health Hospital	Mental health hospital	28
06 Community Hospital	Other	67
07 Older People Hospital	Other	26
08 Multi Service Hospital	Multi-service hospital	9
22 Clinics (Inc. Day Hospitals & Resource Centres)	Other	156
26 Patient Residential Accommodation	Patient residential accommodation	14
41 GP Practice	Other	11
42 Dental Practice	Other	8
43 Pharmacy	Other	1
51 Care Home	Other	23
91 Non NHS Functions	Other	2
98 Non-Operational	Other	25

Table V-A2 WWTW Type to cartography class, with frequency

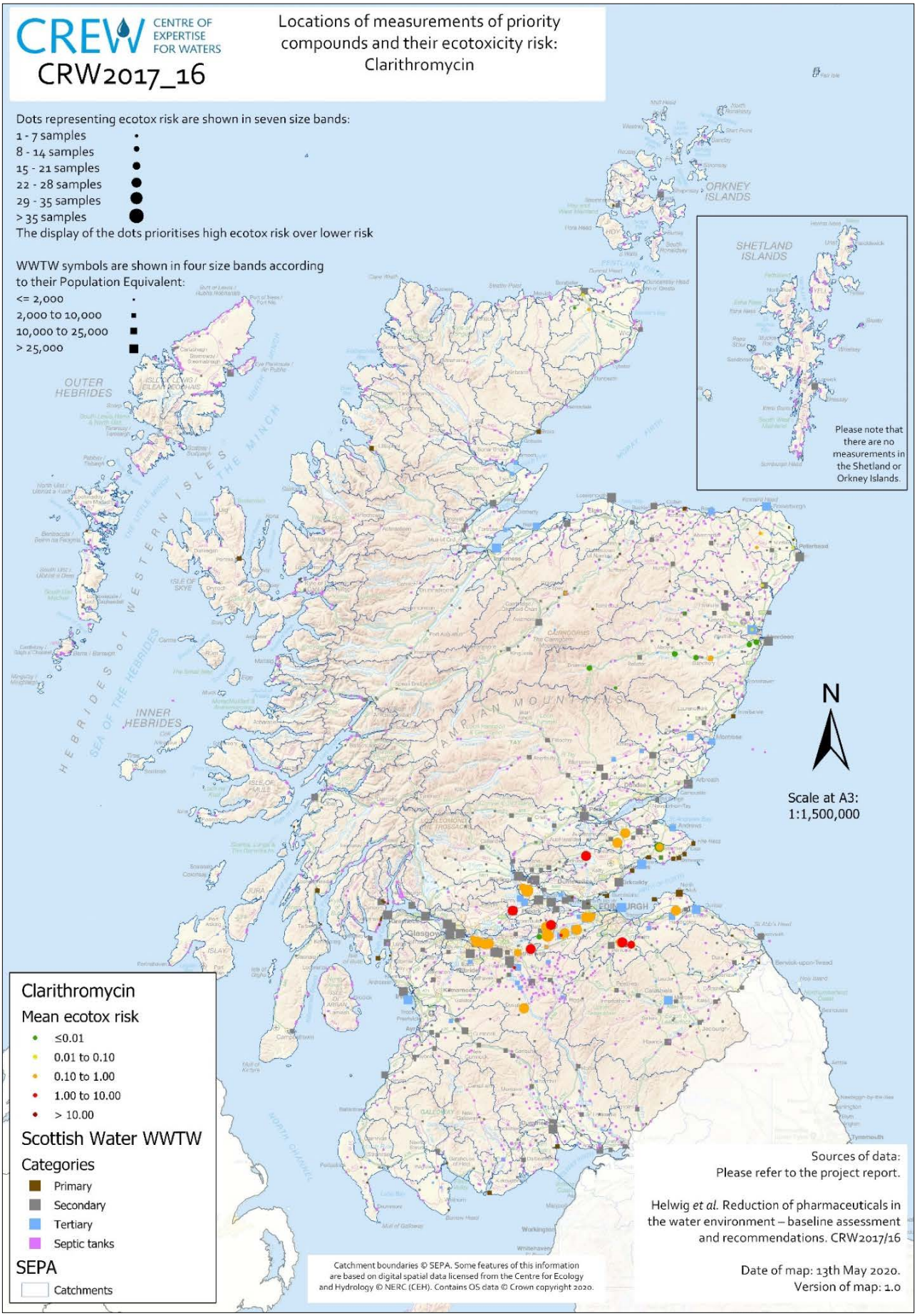
WWTW_Type	Cartography Class	Frequency
ST - SEPTIC TANKS	Septic tanks	1177
SECA - SEC. ACTIVATED SLUDGE	Secondary	186
SECB - SECONDARY BIOLOGICAL	Secondary	295
TE A1 - TERTIARY A1	Tertiary	36
TE B1 - TERTIARY B1	Tertiary	58
PRIM - PRIMARY	Primary	40
TE A2 - TERTIARY A2	Tertiary	27
TE B2 - TERTIARY B2	Tertiary	15
SCR - SCREENED VIA SEA	Primary	3
PRE - PRELIM VIA SEA	Primary	8
SOUNS - UNSCREENED RAW OUTFALL	Primary	13

Gap Analysis map

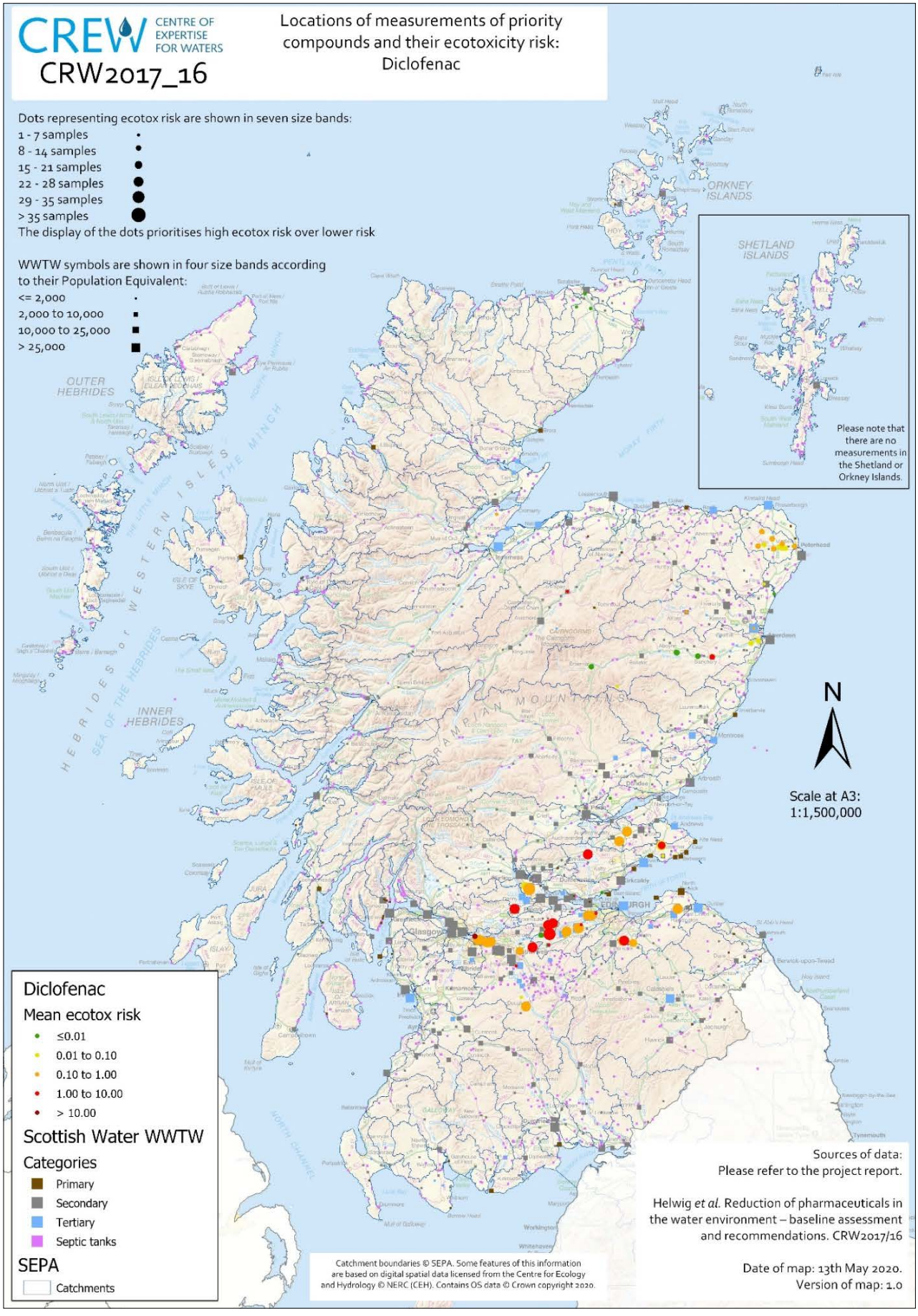


Appendix V Maps – Ecotoxicological Risk

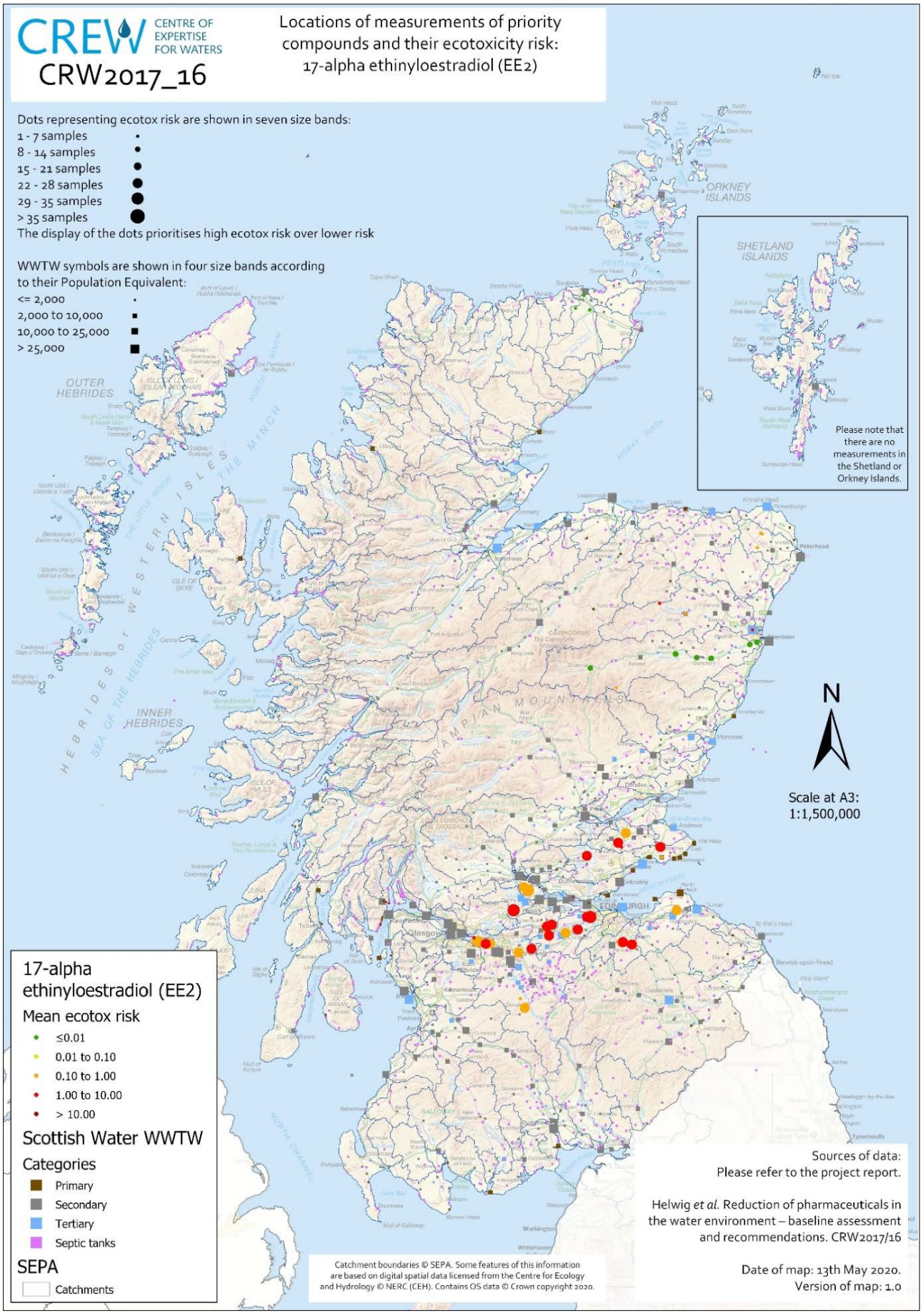
Clarithromycin (Ecotoxicity risk)



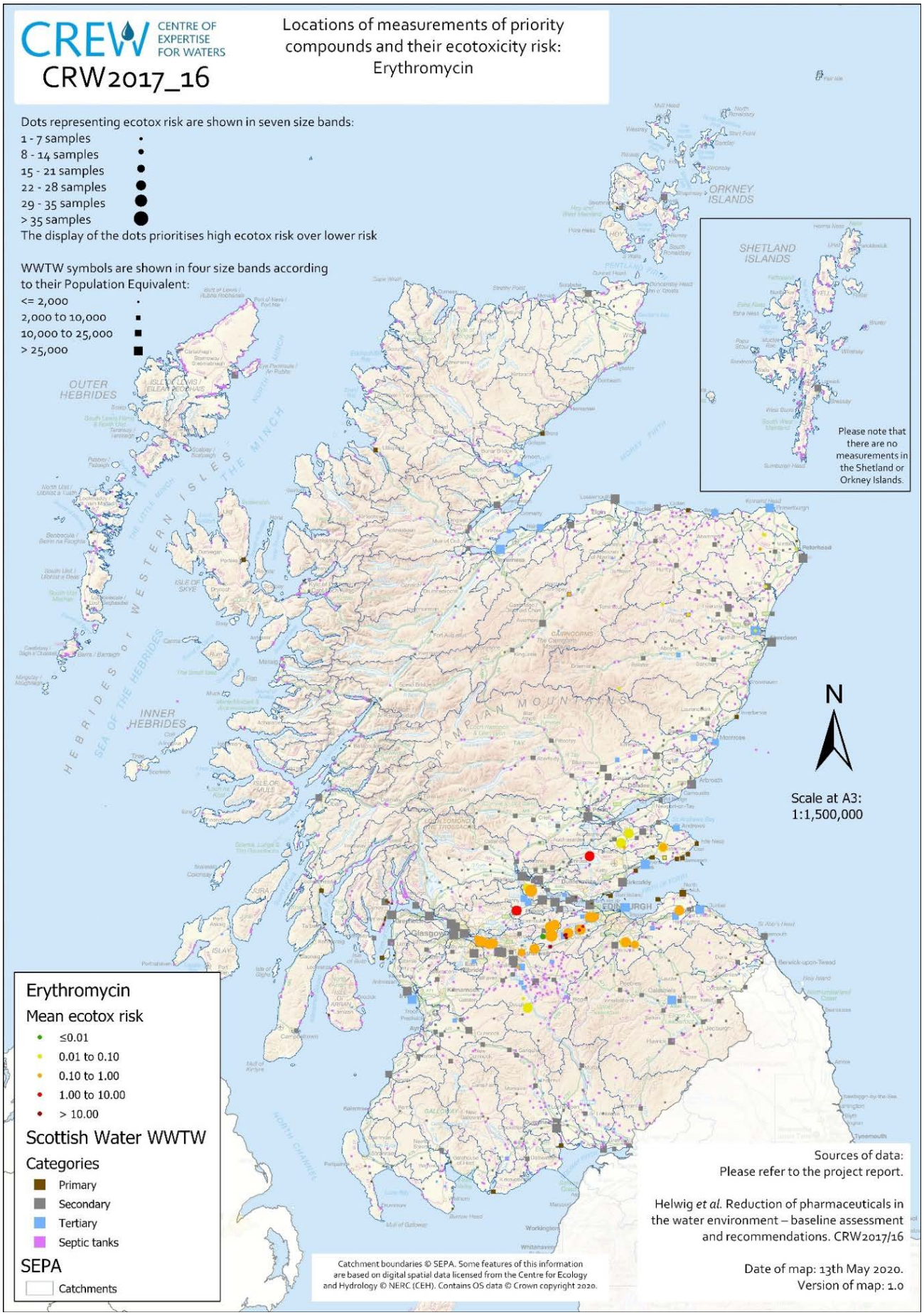
Diclofenac (Ecotoxicity risk)



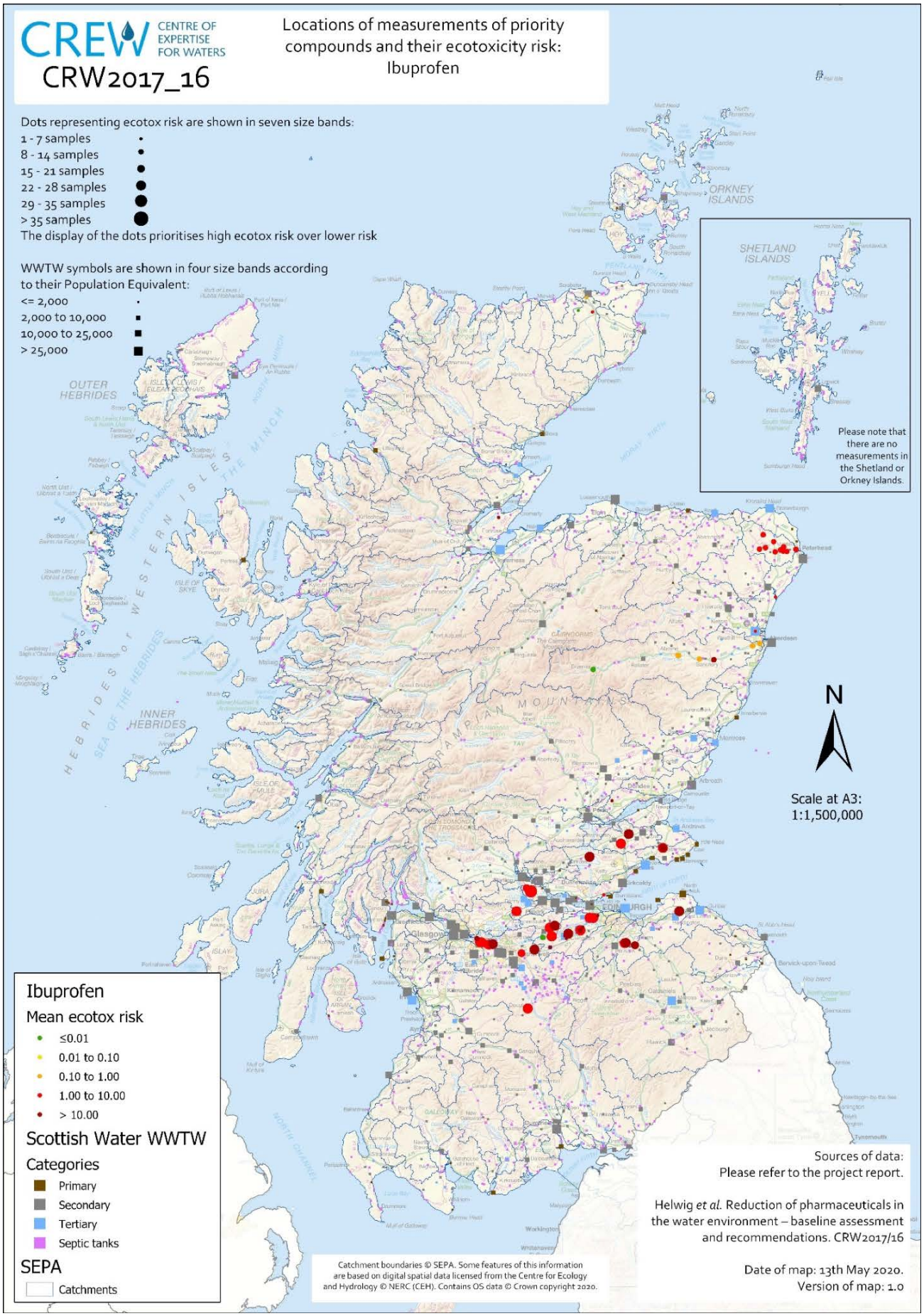
17-alpha ethinyloestradiol (EE2) (Ecotoxicity risk)



Erythromycin (Ecotoxicity risk)

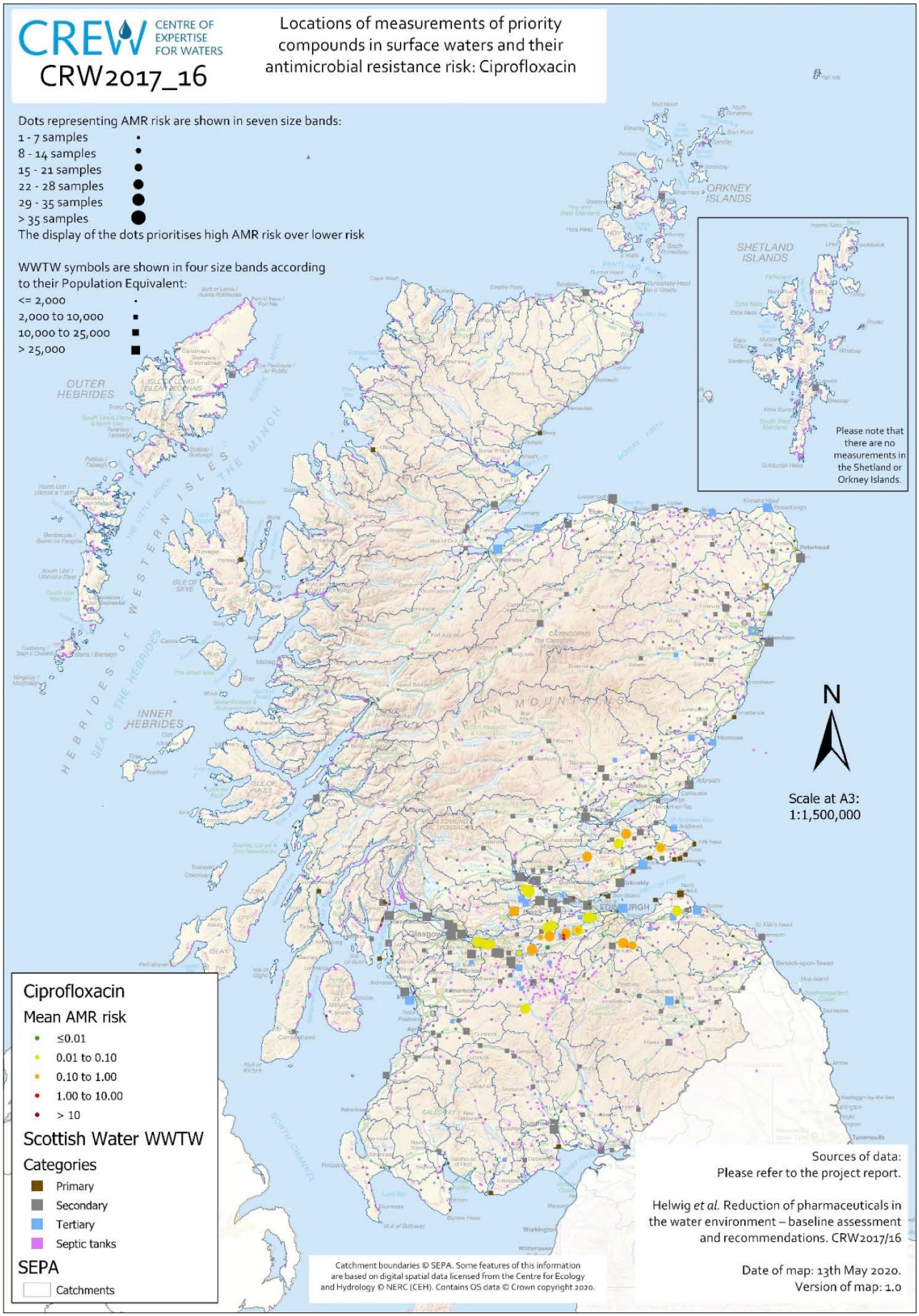


Ibuprofen (Ecotoxicity risk)

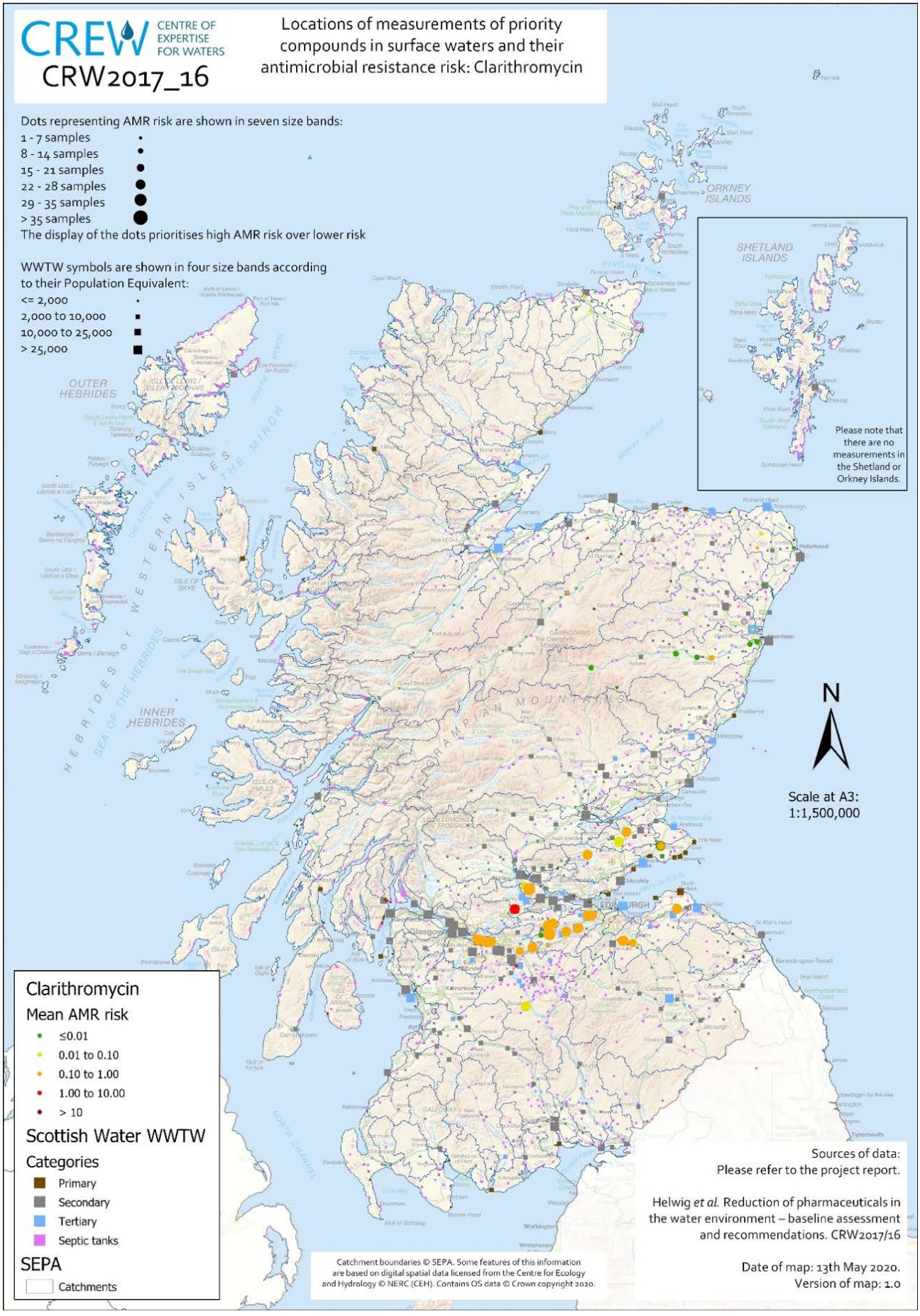


Appendix VI Maps – AMR Risk

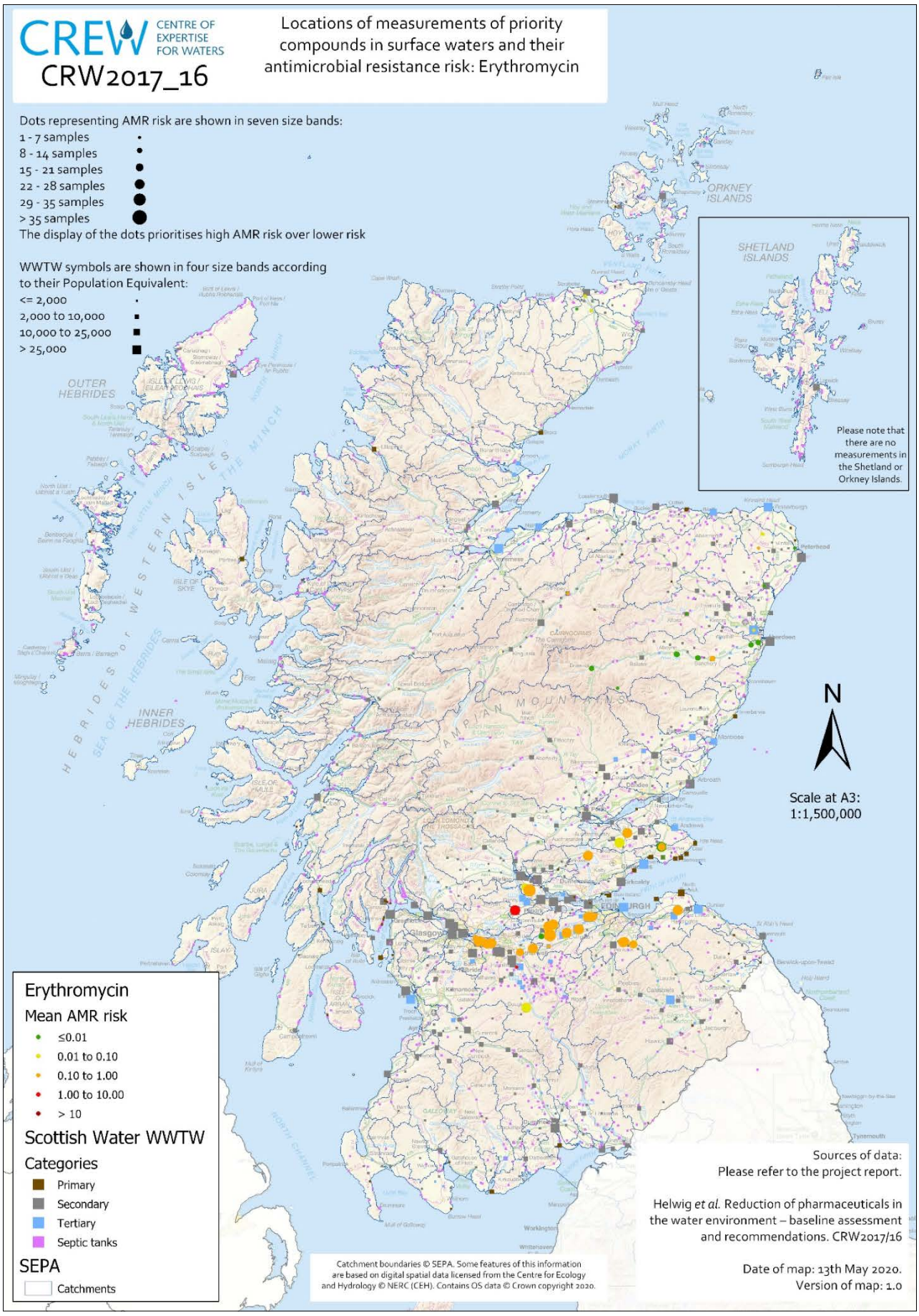
Ciprofloxacin (surface waters)



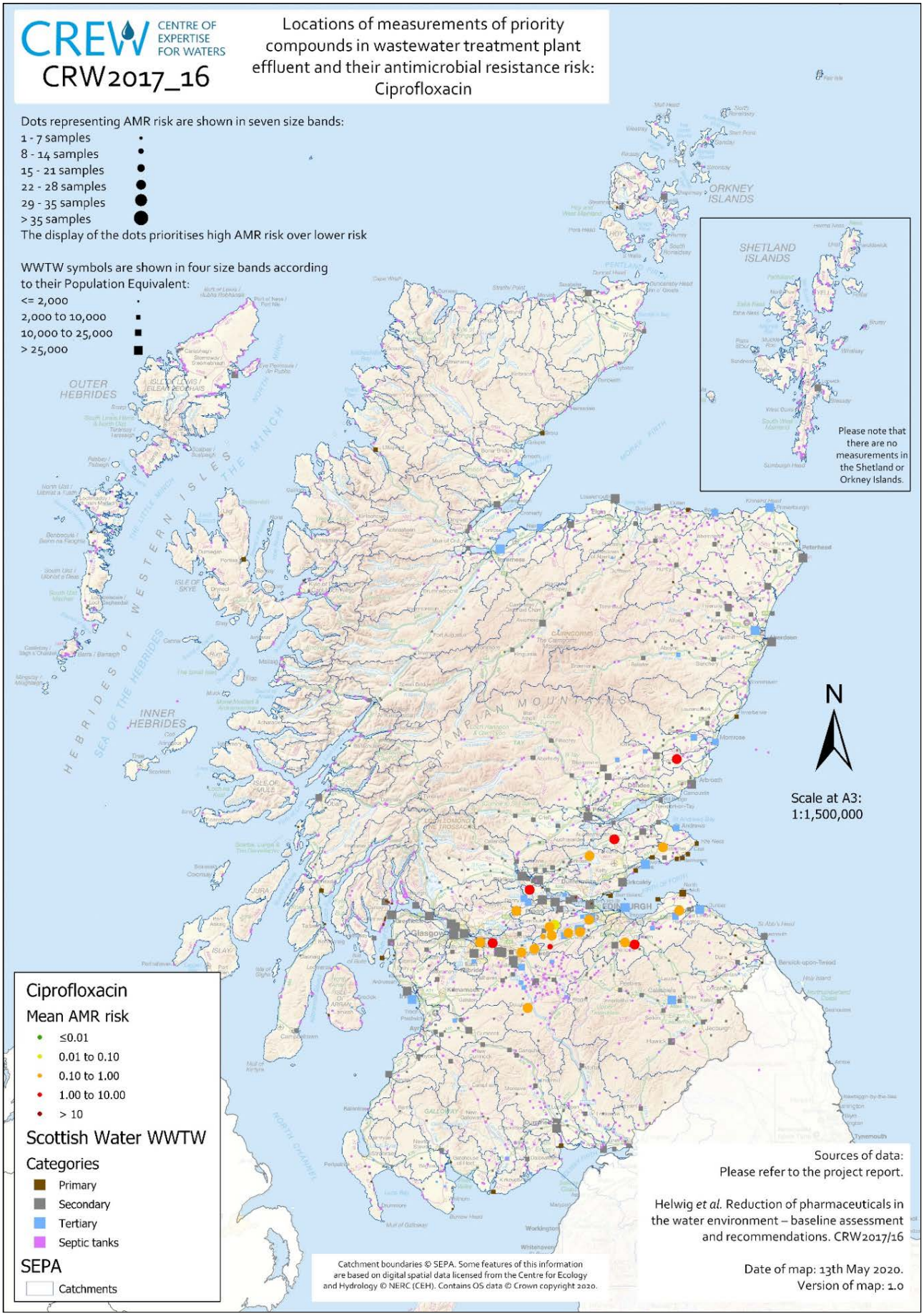
Clarithromycin (surface waters)



Erythromycin (surface waters)



Ciprofloxacin (WWTW effluent)



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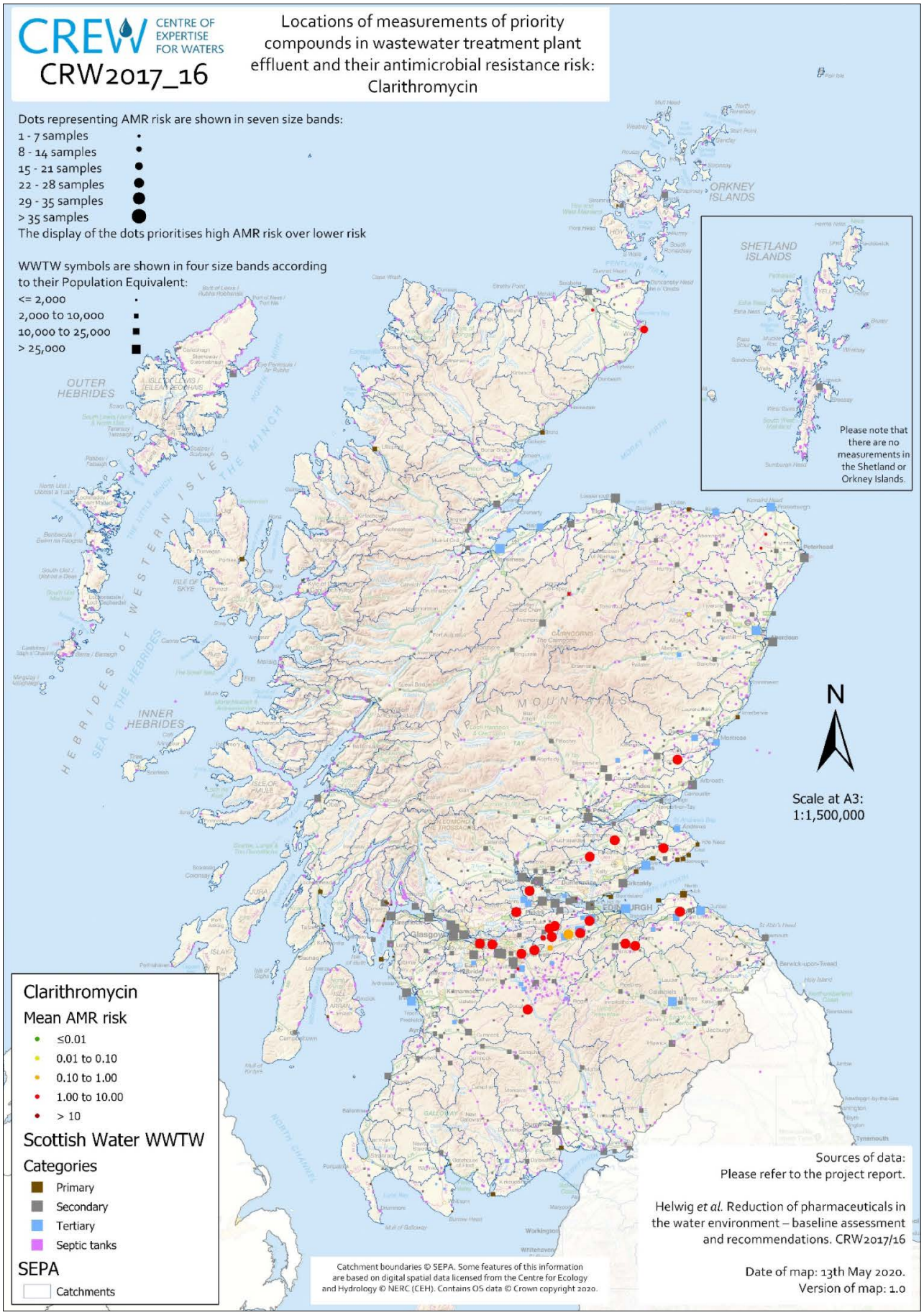
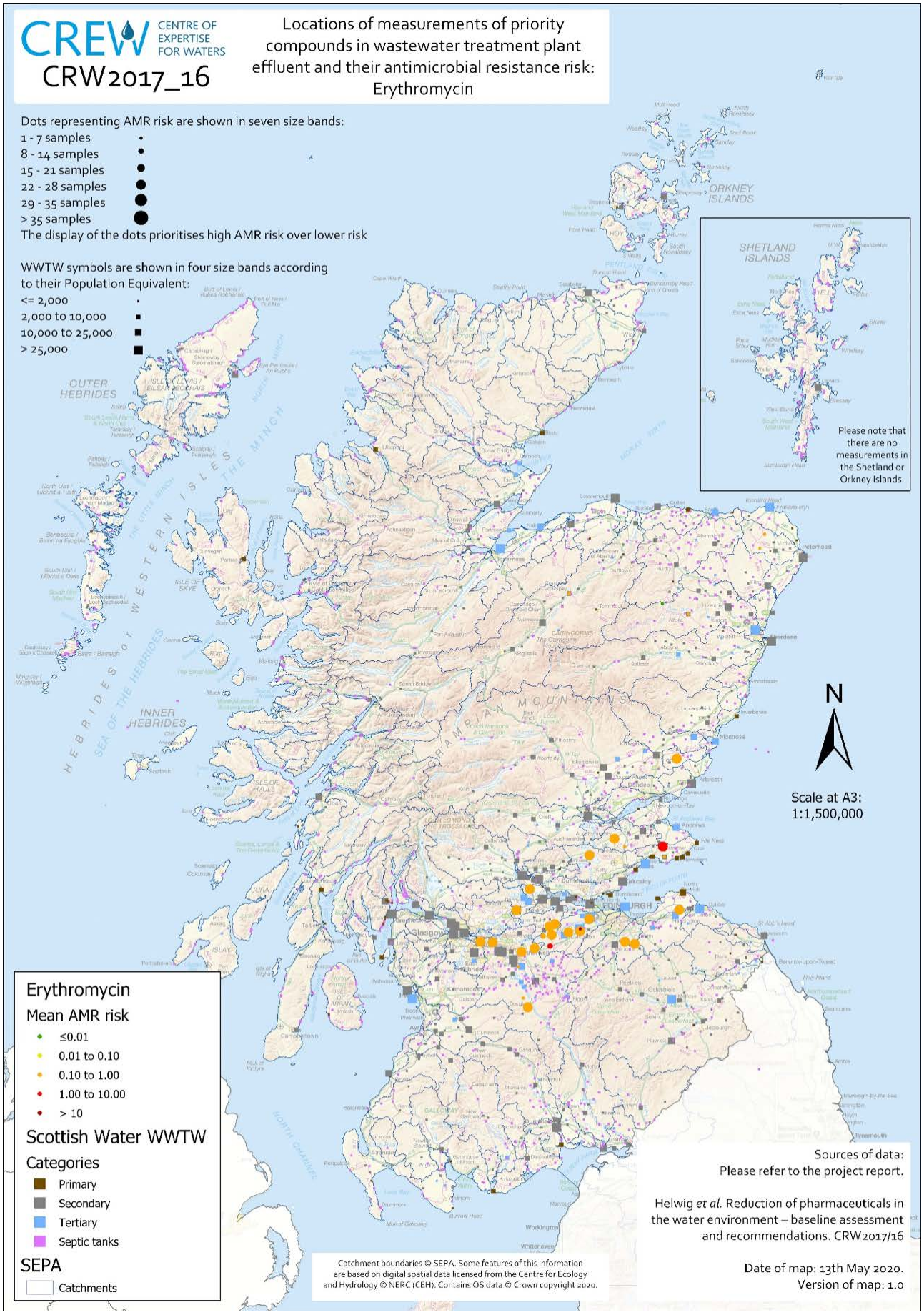
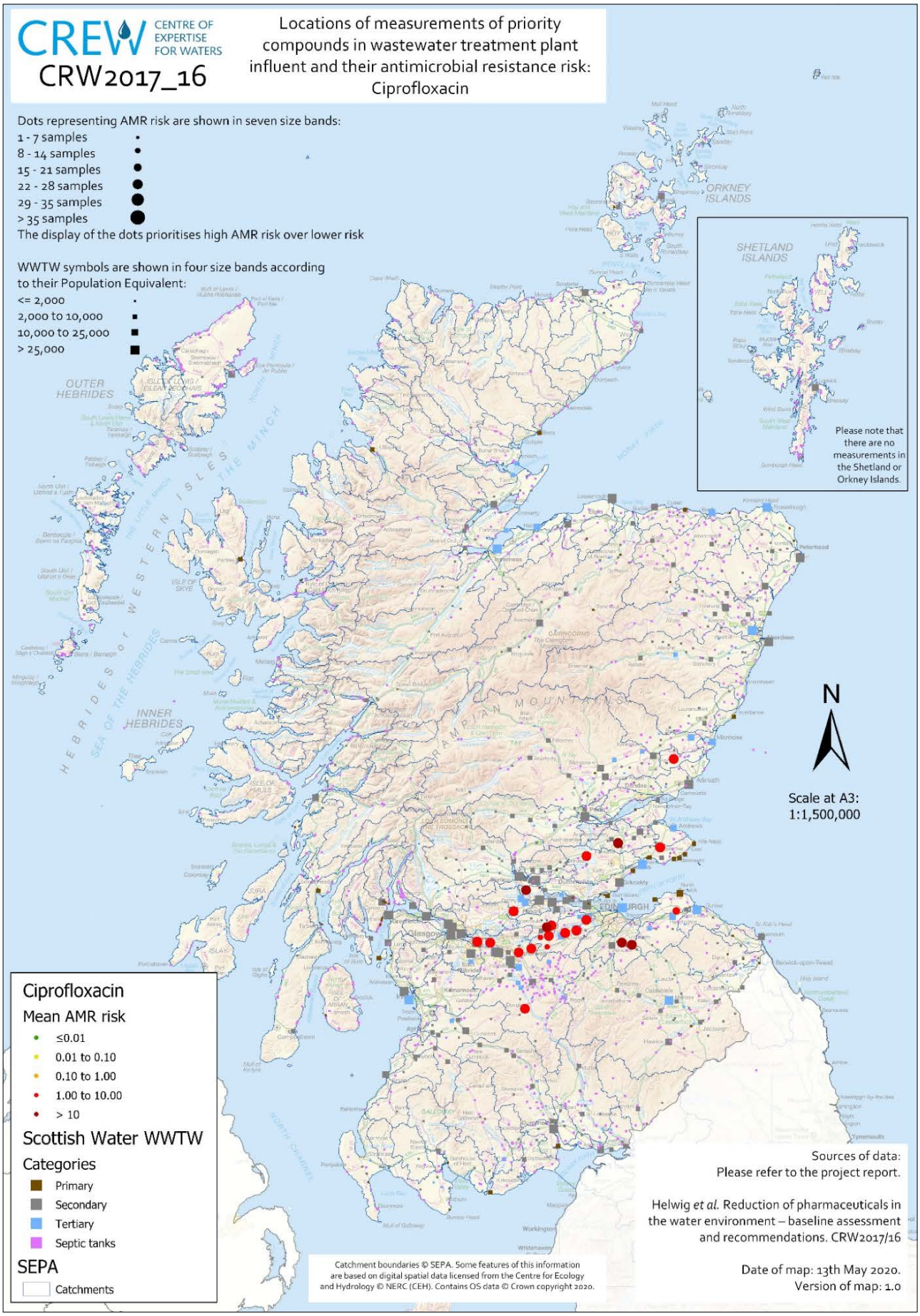


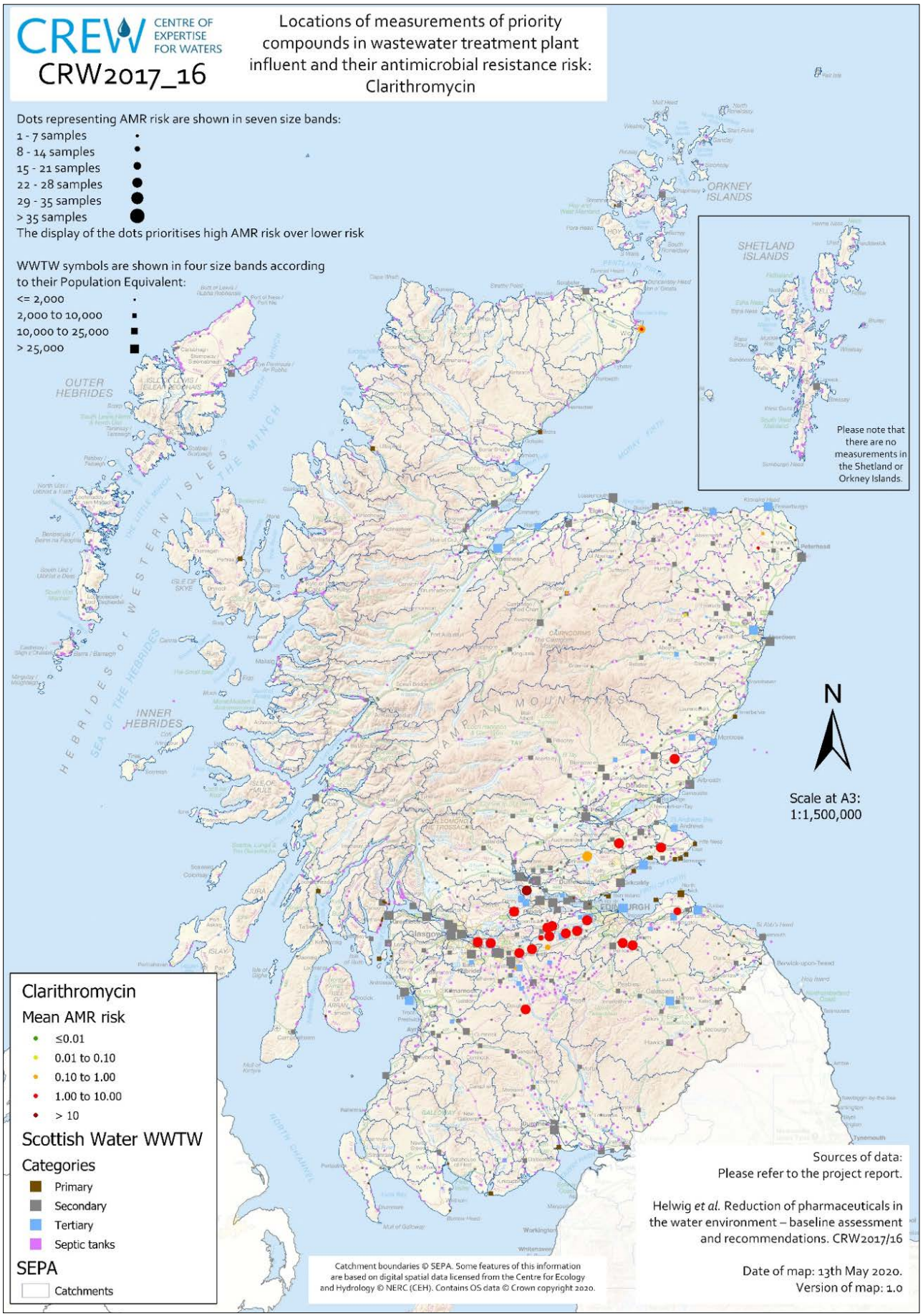
Erythromycin (WWTW effluent)



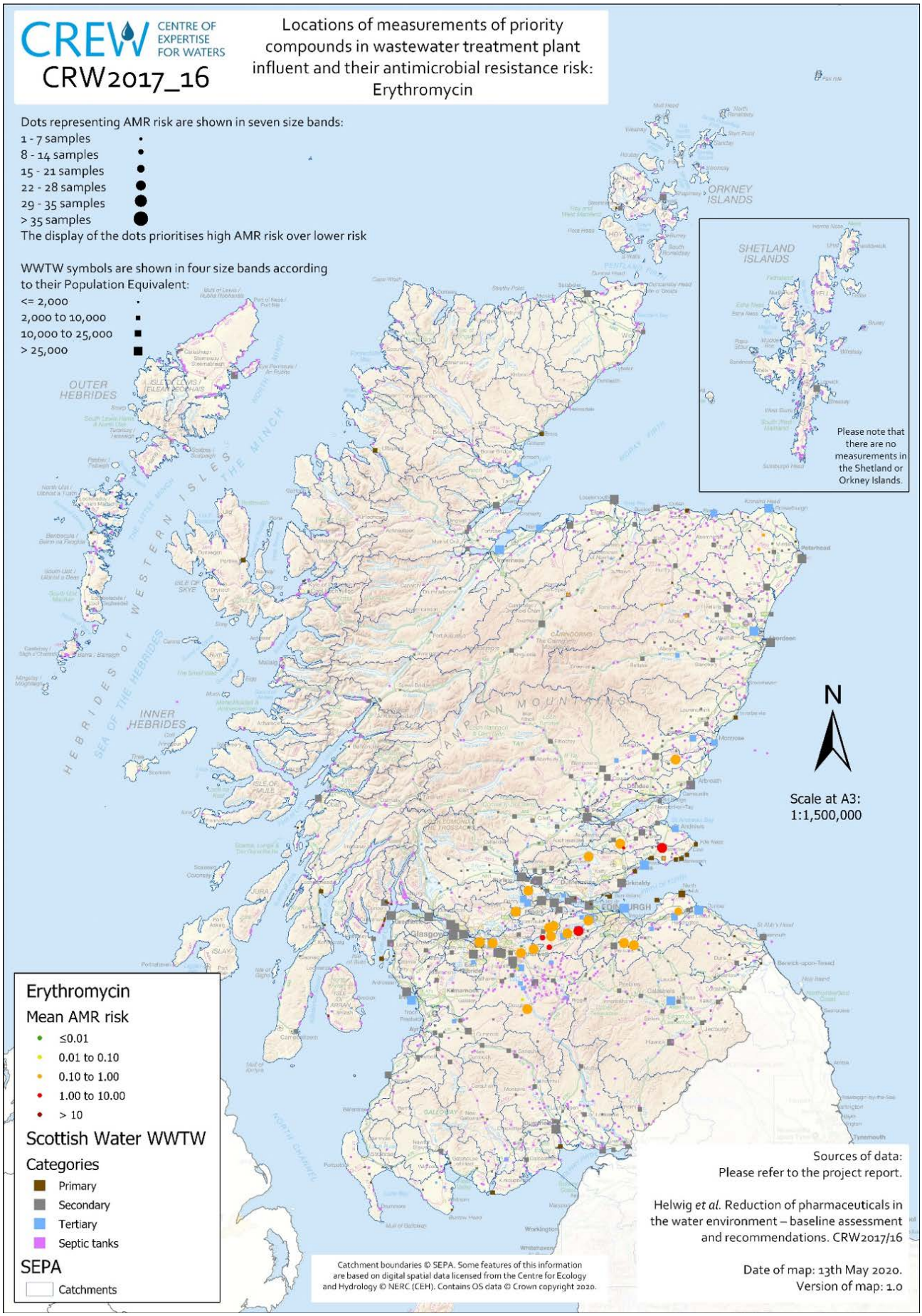
Ciprofloxacin (WWTW effluent)



Clarithromycin (WWTW effluent)



Erythromycin (WWTW effluent)



Appendix VII PNEC values, Assessment Factors and sources

Compounds	PNEC (µg/l) (Values in bold were used for risk calculation)	Modelled value?	AF	References	Species
10,11-Dihydroxycarbazepine or 10,11-Dihydroxycarbamazepine	**Not searched**				
10,11-epoxy-Carbamazepine	**2.5**			23	
17-Alpha ethinyloestradiol (EE2)	**0.000035**			22	
17-beta oestradiol (E2)	**0.0004**			23	
2,6-di-tert-butyl-4-methylphenol	**3.16**			37	
2,6-di-tert-butyl-4-methylphenol	0.191		1000	38	
4-hydroxydiclofenac	**0.05**			39 & 40	
Allopurinol	**0.45**			43	
Amitriptyline	8			31	
Amitriptyline	**2.5**		100	34	
Amitriptyline	10		100	34	Lemna minor
Amlodipine	**0.28**			44	
Amphetamine	**Not searched**				
Amoxicillin	**0.0078**		100	1	Synechoccus leopolensis
Amoxicillin	0.0037		1000	2 & 3	Microcystis aeruginosa
Atenolol	**148**			23	
Atorvastatin	**1.7**			23	
Azithromycin	**0.019**			23	
Benzoylecgonine	**4.9**	ECOSAR		29	
Bezafibrate	**50**		1000	17	Invertebrate
Caffeine	**0.00005**		1000	30	Xenopus laevis
Caffeine	40		1000	5	Ceriodaphnia dubia
Candesartan	**100**			5	
Carbamazepine	**2.5**			23	
Chlorpheniramine	**Not searched**				
Ciprofloxacin	**0.089**			23	
Citalopram	**6.5**	ECOSAR			
Clarithromycin	**0.12**			25	
Clopidogrel	**1.6**			12	
Clotrimazole	**0.014**	QSAR***	1000	12	Green algae*
Cocaine	**4.9**	ECOSAR		29	
Cotinine	**Not searched**				
Cyclophosphamide	**1120**		50	13	Daphnia magna
Dextropropoxyphene	**0.8**			35	
Diazepam	**4.3**		1000	4 &17	Daphnia magna
Diclofenac	**0.05**			39 & 40	
Donepezil	**2.3**			32	
E3 - estriol	**0.06**			36	Gobiocypris rarus
E3 - estriol	0.0075		100	30	Oryzias latipes
Erythromycin	**0.2**			25	
Felodipine	0.05		1000	5	Oncorhynchus mykiss
Felodipine	**20**		10	5	Oncorhynchus mykiss
Fluoxetine	**0.047**			23	

Compounds	PNEC (µg/l) (Values in bold were used for risk calculation)	Modelled value?	AF	References	Species
Fluvoxamine	**1.24**		50	30 & 45	Raphidocelis subcapitata
Fluvoxamine	3051	QSAR^	100	33	Fish*
Fluvoxamine	0.062		1000	34	Raphidocelis subcapitata
Gabapentin	**Not found**				
Glibenclamide	**56.5**		1000	5	Desmodesmus subspicatus
Gliclazide	**Not searched**				
Haloperidol	1.4		1000	5	Danio rerio
Haloperidol	**0.37**		10	5	Raphidocelis subcapitata
Ibuprofen	**0.01**			23	
Ifosfamide	**809.4**		1000	15	Danio rerio
Iohexol	**1000**		1000	5	Salmo Sala
Irbesartan	**704**		10	5	Pimephales promelas
Levonorgestrel	**0.00001**		10	5	Pimephales promelas
Levonorgestrel	≥≥0.00008		10	6	Pimephales promelas
Lidocaine	**32**		1000	5	Daphnia magna
Lorazepam	**2**	ECOSAR	1000	30 & 32	Algae*
Losartan	**1000**		10	5	Pimephales promelas
Meclozine	**0.12**	QSAR***	1000	12	Green algae*
Mefenamic acid	0.79	QSAR***	1000	12	Green algae*
Mefenamic acid	0.428	ECOSAR			Daphnid*
Mefenamic acid	**3.9**		1000	30 & 45	Thamnocephalus platyurus
Mefenamic acid	0.43	ECOSAR	1000	3	
Mesalazine	**10000**				Oncorhynchus tshawytscha
Metformin	**13.45**			23	
Methylparaben	**Not searched**				
N-acetyl sulphamethoxazole	**Not searched**				
Naproxen	**15**		10	5	Daphnia magna
Naproxen	**0.64**			16	
Norerythromycin	**0.2**			23	
Norsertraline	**0.121**			23	
Oestrone (E1)	**0.0036**			25	
Ofloxacin	10		10	9	Cyanobacteria**
Ofloxacin	0.016		1000	14	Cyanobacteria**
Ofloxacin	**0.5**		10	14	Cyanobacteria**
Omeprazole	**41.9**		1000	5	Danio rerio
Orlistat	**0.032**		50	28	Daphnia magna
Orthoatorvastatin	**1.7**			23	
ortho-Hydroxyatorvastatin	**1.7**			23	
Oxazepam	32	QSAR***	1000	12	Green algae*
Oxazepam	**4.3**			29	
Oxytetracycline	0.207		1000	8	Microcystis aeruginosa

Compounds	PNEC (µg/l) (Values in bold were used for risk calculation)	Modelled value?	AF	References	Species
Oxytetracycline	**18**		10	9	Cyanobacteria**
Paracetamol	**46**		10	5	Pimephales promelas
Paracetamol	9.2		1000	5	Danio rerio
para-Hydroxyatorvastatin	**1.7**			23	
Paroxetine	0.14		1000	5	Scenedesmus subspicatus
Paroxetine	**8.8**		50	30 & 45	Ceriodaphnia dubia
Povidone Iodine	**1.84**			46	
Propranolol	**0.1**			23	
Ranitidine	**0.31**			23	
Risperidone	**5.8**		1000	5	Lepomis macrochirus
Roxithromycin	**0.047**		1000	7	Raphidocelis subcapitata
Roxithromycin	**1**		10	7	Raphidocelis subcapitata
Salbutamol	**Not searched**				
Sertraline	**0.121**			23	
Sulfamethoxazole	0.118		50	13	Synechococcus leopolensis
Sulfamethoxazole	0.027		1000	14	Cyanobacteria**
Sulfamethoxazole	**0.59**		10	14	Cyanobacteria**
Tamoxifen	**0.49**			23	
Tazobactam	**0.06**			47	
Tetracycline	0.09		1000	8	Microcystis aeruginosa
Tetracycline	**3.2**		10	9	Cyanobacteria**
Tramadol	**64**			18	
Triclosan	0.05		10	19	Scenedesmus subspicatus
Triclosan	**0.02**		10	20	Raphidocelis subcapitata
Triclosan	0.0044		1000	21	Raphidocelis subcapitata
Triclosan	0.0007		1000	21	Scenedesmus subspicatus
Trimethoprim	3		1000	10	Oncorynchus mykiss
Trimethoprim	**0.0058**		50	30 & 45	Dreissena polymorpha
Trimethoprim	100		10	9	Anabaena flos-aquae
Venlafaxine	**0.013**	ECOSAR	1000	11	Cladoceran*
X-ray contrast media iopromide(iodine-123, -225, -129, -131)	**> >10000**		100	41	Daphnia magna
X-ray contrast media iopromide(iodine-123, -225, -129, -131)	8.8	ECOSAR	100	42	Green algae*

Notes

* QSAR and similar prediction tools use generic descriptors - "Green algae"; "Daphnia" or "fish"

** Publication derived data from lab experiments but only discussed data for generic type

*** QSAR models selected were set up for neutral organic molecules and use the octanol-water partition coefficient (Kow) as hydrophobicity descriptor.

^ PNEC values estimated using chronic toxicity for fish values (obtained from PBT Profiler) divided by an assessment factor of 100

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Appendix VIII Antibacterial properties of non-antibiotic pharmaceuticals: a literature review

MEDLINE search

Lucyna Gozdzielewska, Lesley Price

Search methods

MEDLINE database was chosen because it contains a large number of peer-reviewed journals from around the world, covering a broad range of biomedical and health topics. MEDLINE was searched on the 27th August 2019 for records on antibacterial effects of non-antibiotic drugs of interest (listed in Appendix VIII.1). A mixture of MeSH terms and free text words, including the generic name, compound name and brand names of each drug were combined. To limit the number of irrelevant hits, the search was limited by excluding records related to drug interactions and adverse drug reactions. No limiters were applied to the publication date, language or study design. The full search strategy is presented in Appendix VIII.2. Titles and abstracts of the identified records were screened for relevance. Studies investigating antibiotic modulating effect of on-antibiotic drugs or effect on the immune response were not considered. Content analysis was used to identify pharmaceuticals that showed antibacterial properties with findings summarised below.

Results

A total of 1446 records were identified in the electronic search. After screening the titles and abstracts, 116 studies were considered relevant. Amongst these, 12 records investigated antibacterial properties of more than one non-antibiotic drugs of interest.

Lidocaine (n=44)

Lidocaine was the most commonly investigated, with 44 studies investigating its antibacterial properties. Amongst these, 36 demonstrated antibacterial properties of lidocaine. Furthermore, of the 44 studies on lidocaine, four (Gajraj et al., 1998; Sakuragi et al., 1999; Vidovich, M. I., et al., 1999; Wachowski, I., et al. 1999) focused specifically on the effect of lidocaine on bacterial growth in Propofol – an anaesthesia drug that was previously found to enhance microbial growth when contaminated. However, only one study (Gajraj et al., 1998) showed antibacterial activity of lidocaine in mixtures with propofol, and one (Sakuragi et al., 1999) showed bacteriostatic rather than bactericidal effect when tested against E.coli.

Non-steroid anti-inflammatory drugs: Ibuprofen (n=19), Diclofenac (n=16) & Naproxen (n=2)

Antibacterial properties of Ibuprofen were investigated in 19 studies, amongst which only 3 showed no antibacterial effect of Ibuprofen against six common periodontal pathogens (Hersh et al., 1991), *Brucella* species (Muñoz-Criado et al., 1996) and against urinary tract infection isolates (Whiteside et al., 2019). Sixteen studies investigated antibacterial properties of diclofenac and all sixteen showed its antibacterial l properties against a variety of strains and isolates. Similarly, Naproxen demonstrated an anti-microbial effect in two studies (Kruszewska et al., 2000; Kruszewska et al., 2002).

Antidepressants: Fluoxetine (n=6), Sertraline (n=6), Venlafaxine (n=1) & Escitalopram (n=2)

Fluoxetine and Sertraline were investigated for their antibacterial properties in 6 studies each, and in both cases, all six studies demonstrated antibacterial properties of these antidepressants. Similarly, Escitalopram (Cussotto et al., 2019; Valipour et al., 2019) and analogues of Venlafaxine, rather than Venlafaxine itself, (Kavitha et al., 2006), demonstrated antibacterial properties.

Analgesics: Paracetamol (n=5) & Tramadol (n=3)

For Paracetamol, four out of five studies showed its antibacterial effect (Akhter et al., 2010; Al-Janabi, 2010; Sheu et al., 1975; Vijayashree, 2019) and for Tramadol two out of three studies demonstrated antibacterial properties (Kruszewska et al., 2002; Tamanai-Shacoori et al., 2007) and one did not (Farzam et al., 2018).

Cardiac drugs: Atorvastatin (n=5) & Propranolol (n=1)

For Atorvastatin, a statin, two (Ko et al., 2017; Masadeh et al., 2012) out of five studies demonstrated its antibacterial effect, while for Propranolol three studies did so (Jerwood et al., 2008; Kapoor et al., 2018; Kruszewska et al., 2004).

Anti-inflammatory or anti-oxidant: Butylated hydroxytoluene (n=5)

Five studies investigated Butylated hydroxytoluene (Ayaz et al., 1980; Chew et al., 1985; Gailani et al., 1984; Santhakumari et al., 2018; Turcotte et al, 1978) and all confirmed its antibacterial properties.

Ranitidine (n=4)

Four studies tested antibacterial properties of Ranitidine of which two, demonstrated such properties (Alarcón et al., 1999; Brorson et al., 2001). Ranitidine was also found to have an antibiotic-modulating effect when included in the multidrug regimen for the treatment of Helicobacter Pylori eradication; however modulating effect was beyond the scope of this literature search.

Hypoglycaemic drugs: Metformin (n=3) & Glibenclamide (n=1)

Metformin demonstrated an antibacterial effect (Courtois et al., 2018; Kapoor et al., 2018; Malik et al., 2018) but Glibenclamide did not have such an effect (Koh et al., 2013); however, the latter was tested against one type of bacteria only (Burkholderia pseudomallei).

Chemotherapy drugs: Tamoxifen (n=2) & Cyclophosphamide (n=1)

Tamoxifen showed an antibacterial effect in two studies (El Arbi et al., 2014; Montoya et al 2018) but Cyclophosphamide only minimal antibacterial activity (Peiris et al., 1993).

Antipsychotic drugs: Flupenthixol (n=2) & Haloperidol (n=1)

Both Flupenthixol (Jeyaseeli et al., 2006; Kristiansen et al., 1986) and Haloperidol (Mortensen et al., 1992) showed antibacterial effect in two and one study respectively.

Hormone replacement therapy: Estradiol (n=1)

The hormone Estradiol as opposed to a specific drug demonstrated antibacterial effect in one study. (Hosoda et al., 2011.

Furthermore, when screening the search results it was identified that Estradiol, Metformin, and Glibenclamide were found to influence the immune responses, while statins (Atorvastatin, Simvastatin) were found to have a synergistic effect when administered with antibiotic in addition to the ability to stimulate the host immune system. However, these properties are beyond the scope of this review.

Appendix VIII.1. List of drugs included in the search

2,6-di-tert-butyl-4-methylphenol
Atenolol
Atorvastatin
Bezafibrate
Carbamazepine
Citalopram
Cyclophosphamide
Dextropropoxyphene
Diazepam
Diclofenac
Escitalopram
Estradiol (E2)
Estriol (E3)
Estrone (E1)
Ethinylestradiol (EE2)
Felodipine
Fluoxetine
Flupenthixol
Glibenclamide
Haloperidol
Ibuprofen
Ifosfamide
iodine-123
Iodine-125
Iodine-129
Iodine-131
Irbesartan
Levonorgestrel
Lidocaine
Meclozine
Mefanamic acid
Metformin
Naproxen
Oxazepam
Paracetamol
Propranolol
Ranitidine
Risperidone
Sertraline
Tamoxifen
Tramadol
Venlafaxine

Appendix VIII.2. Search strategy for MEDLINE

1. Non-antibiotic drugs: mesh terms

MH "Diclofenac" OR (MH "Ibuprofen") OR (MH "Ethinyl Estradiol") OR (MH "Naproxen") OR (MH "Levonorgestrel") OR (MH "Estradiol") OR (MH "Estrone") OR (MH "Estriol") OR (MH "Citalopram") OR (MH "Fluoxetine") OR (MH "Sertraline") OR (MH "Venlafaxine Hydrochloride") OR (MH "Felodipine") OR (MH "Irbesartan") OR (MH "Atorvastatin") OR (MH "Propranolol") OR (MH "Atenolol") OR (MH "Flupenthixol") OR (MH "Haloperidol") OR (MH "Risperidone") OR (MH "Diazepam") OR (MH "Oxazepam") OR (MH "Glyburide") OR (MH "Metformin") OR (MH "Carbamazepine") OR (MH "Tamoxifen") OR (MH "Cyclophosphamide") OR (MH "Ifosfamide") OR (MH "Dextropropoxyphene") OR (MH "Acetaminophen") OR (MH "Tramadol") OR (MH "Lidocaine") OR (MH "Meclizine") OR (MH "Ranitidine") OR (MH "Bezafibrate") OR (MH "Butylated Hydroxytoluene") OR (MH "Iodine Isotopes")

2. Non-antibiotic drugs: free text words

Diclofenac OR Voltaren OR Cataflam OR Cambia OR Zorvolex OR Ibuprofen OR Brufen OR Anadin OR "Feminax Express" OR Ibucalm OR Ibular OR Nurofen OR Cuprofen OR Calprofen OR Fenpaed OR Ibugel OR Ibuleve OR Phorpain OR Fenbid OR Flarin OR Motrin OR Advil OR IBU OR "Mefanamic acid" OR "Mefenamic acid" OR Ponstan OR Ponstel OR Naproxen OR "Feminax Ultra" OR Naprosyn OR Nexocin OR Stirlescent OR Aleve OR Anaprox OR "Ethinylestradiol (EE2)" OR "Ethinylestradiol ee2" OR Ethinylestradiol OR "Ethinyl estradiol" OR Estinyl OR Levonorgestrel OR Norgeston OR Emerres OR Ezinelle OR Levonelle OR Levonorgestrel OR Melkine OR Upostelle OR Mirena OR "Estradiol (E2)" OR estradiol OR "Estradiol e2" OR Oestradiol OR FemSeven OR Estraderm OR Bedol OR Vagifem OR Elleste OR Sandrena OR Progynova OR Estring OR Evorel OR Estradot OR Oestrogel OR Zumenon OR Vagifem OR Evorel OR Estradot OR "Estrone (E1)" OR "estrone e1" OR Estrone OR Kestrone OR Estragyn OR Aquest OR "Estriol (E3)" OR "estriol e3" OR estriol OR Ovestin OR Oestriol OR Citalopram OR Cipramil OR Celexa OR Escitalopram OR Cipralex OR Fluoxetine OR Olena OR Prozac OR Prozep OR Rapiflux OR Sarafem OR Selfemra OR Sertraline OR Lustral OR Zoloft OR Venlafaxine OR Venlalic OR Sunveniz OR Venladex OR ViePax OR Sunveniz OR Venlalic OR Apclaven OR Majoven OR Vencarm OR Venlablue OR Alventa OR Apclaven OR Depefex OR Efexor OR Politid OR Tonpular OR Venaxx OR Venlasov OR Vensir OR Venzip OR Vencarm OR Effexor OR Felodipine OR Cardioplen OR Felotens OR Folpik OR Neofel OR Parmid OR Plendil OR Vascalpha OR Irbesartan OR Aprovel OR Ifirmasta OR Avapro OR Atorvastatin OR Lipitor OR Propranolol OR Inderal OR Inderal OR Hemangeol OR InnoPran OR Bedranol OR "Beta-Prograne" OR Angilol OR Atenolol OR Tenormin OR Flupenthixol OR Flupentixol OR Fluanxol OR Depixol OR Navane OR aractan OR "Thiothixene HCl Intensol" OR Haloperidol OR Halkid OR Haldol OR Serenace OR Risperidone OR Risperdal OR Perseris OR Diazepam OR Diazemuls OR Stesolid OR Valium OR Diastat OR Zetran OR Oxazepam OR Serax OR Glibenclamide OR Glyburide OR DiaBeta OR "Glynase PresTab" OR Micronase OR Metformin OR Bolamyn OR Glucient OR Glucophage OR Meijumet OR Metabet OR Metuxtan OR Sukkarto OR Yaltormin OR Glumetza OR Fortamet OR Carbamazepine OR Tegretol OR Carbagen OR Epitol OR Carbatrol OR Tamoxifen OR Nolvadex OR Tamofen OR Cyclophosphamide OR Cytoxan OR Neosar OR Ifosfamide OR Ifex OR Dextropropoxyphene OR Destropropoxifene OR Paracetamol OR Acetaminophen OR Anadin OR Hedex OR Mandanol OR Panadol OR Paravict OR Alvedon OR Calpol OR "Junior Parapaed" OR Altridexamol OR Perfalgan OR Tylenol OR Mapap OR Tramadol OR Zydol OR Brimisol OR Invodol OR Mabron OR Maneo OR Marol OR Tilodol OR Tradorec OR Tramulief OR Zytram OR Zamadol OR Maxitram OR Tramquel OR Ultram OR Tramal OR Ultram OR Lidocaine OR "LMX 4" OR Versatis OR Xylocaine OR Ralvo OR Vagisil OR Xylocaine OR Nervocaine OR Lidoject OR Meclozine OR Meclizine OR Antivert OR Bonine OR D-Vert OR "Dramamine Less Drowsy" OR Driminate OR Meclicot OR Medivert OR "Ru-Vert-M" OR "Meni-D" OR Ranitidine OR Gavilast OR Ranicalm OR Zantac OR Bezafibrate OR Bezalip OR Fibrazate OR "2,6-di-tert-butyl-4-methylphenol" OR "Butylated hydroxytoluene" OR "iodine-123" OR "iodine I-123" OR "Sodium Iodide" OR "Iodine-125" OR "Iodine I-125" OR "Iodine-129" OR "Iodine I-129" OR "Iodine-131" OR "Iodine I-131"

3. Antibacterial properties

Antibacterial* OR antimicrobial* OR "anti-microbial*" OR antiinfection* OR "anti-infection*" OR "anti-infective" OR antiinfective OR antibacterial* OR "anti-bacterial*" OR bactericidal OR germicidal

4. Terms for exclusion

Mesh terms: (MH "Drug Interactions") OR (MH "Drug-Related Side Effects and Adverse Reactions") OR (MH "Mycoses") OR (MH "Neutropenia")

Search combination

((1 OR 2) AND 3) NOT 4

Appendix VIII.3. Full list of identified studies per drug

2,6-di-tert-butyl-4 methylphenol (n=5)

1. Ayaz, M., et al. (1980). "Antimicrobial Effect of Butylated Hydroxyanisole and Butylated Hydroxytoluene on Staphylococcus aureus 1." Journal Of Food Protection 43(1): 4-6.
2. Chew, B. P., et al. (1985). "In vitro growth inhibition of mastitis causing bacteria by phenolics and metal chelators." Journal Of Dairy Science 68(11): 3037-3046.
3. Gailani, M. B. and D. Y. C. Fung (1984). "Antimicrobial Effects of Selected Antioxidants in Laboratory Media and in Ground Pork." Journal Of Food Protection 47(6): 428-433.
4. Santhakumari, S., et al. (2018). "In vitro and in vivo effect of 2,6-Di-tert-butyl-4-methylphenol as an antibiofilm agent against quorum sensing mediated biofilm formation of Vibrio spp." International Journal Of Food Microbiology 281: 60-71.
5. Turcotte, P. and S. A. Saheb (1978). "[Antimicrobial activity of phenolic antioxidants]." Canadian Journal Of Microbiology 24(11): 1306-1320.

Atorvastatin (n=5)

1. Coban, A. Y., et al. (2010). "[Investigation of the in vitro antibacterial effects of statins]." Mikrobiyoloji Bulteni 44(1): 161-163. (Did not show antimicrobial effect)
2. Graziano, T. S., et al. (2015). "Statins and Antimicrobial Effects: Simvastatin as a Potential Drug against Staphylococcus aureus Biofilm." Plos One 10(5): e0128098-e0128098. (Did not show antimicrobial effect, but was tested against MRSA and MSSA strains only)
3. Ko, H. H. T., et al. (2017). "Statins: antimicrobial resistance breakers or makers?" Peerj 5: e3952-e3952. (Review)
4. "Masadeh, M., et al. (2012). "Antibacterial activity of statins: a comparative study of atorvastatin, simvastatin, and rosuvastatin." Annals Of Clinical Microbiology And Antimicrobials 11: 13-13.
5. Welsh, A.-M., et al. (2009). "Antimicrobial action of atorvastatin and rosuvastatin." Pathology 41(7): 689-691. (Showed bacteriostatic, rather than bactericidal effect)

Cyclophosphamide (n=1)

1. Peiris, V. and B. A. Oppenheim (1993). "Antimicrobial activity of cytotoxic drugs may influence isolation of bacteria and fungi from blood cultures." Journal Of Clinical Pathology 46(12): 1124-1125 (Showed minimal antimicrobial activity)

Diclofenac (n=16)

1. Alqahtani, F. Y., et al. (2019). "Preparation, characterization, and antibacterial activity of diclofenac-loaded chitosan nanoparticles." Saudi Pharmaceutical Journal: SPJ: The Official Publication Of The Saudi Pharmaceutical Society 27(1): 82-87.
2. Annadurai, S., et al. (1998). "Antibacterial activity of the antiinflammatory agent diclofenac sodium." Indian Journal Of Experimental Biology 36(1): 86-90.
3. Annadurai, S., et al. (2002). "Experimental studies on synergism between aminoglycosides and the antimicrobial antiinflammatory agent diclofenac sodium." Journal Of Chemotherapy (Florence, Italy) 14(1): 47-53.
4. Bandara, B. M. K., et al. (2004). "Non-steroidal anti inflammatory agents decrease bacterial colonisation of contact lenses and prevent adhesion to human corneal epithelial cells." Current Eye Research 29(4-5): 245-251.
5. Chockattu, S. J., et al. (2018). "Comparison of anti-bacterial efficiency of ibuprofen, diclofenac, and calcium hydroxide against Enterococcus faecalis in an endodontic model: An in vitro study." Journal Of Conservative Dentistry: JCD 21(1): 80-84.
6. Dastidar, S. G., et al. (2000). "The anti-bacterial action of diclofenac shown by inhibition of DNA synthesis." International Journal Of Antimicrobial Agents 14(3): 249-251.
7. Dutta, N. K., et al. (2007). "Activity of diclofenac used alone and in combination with streptomycin against Mycobacterium tuberculosis in mice." International Journal Of Antimicrobial Agents 30(4): 336-340.
8. Dutta, N. K., et al. (2008). "In vitro efficacy of diclofenac against Listeria monocytogenes." European Journal Of Clinical Microbiology & Infectious Diseases: Official Publication Of The European Society Of Clinical Microbiology 27(4): 315-319.
9. Guzel, M., et al. (2010). "Clinical efficacy of diclofenac sodium and flunixin meglumine as adjuncts to antibacterial treatment of respiratory disease of calves." Australian Veterinary Journal 88(6): 236-239.
10. Kahlous, N. A., et al. (2017). "Using Chemoinformatics, Bioinformatics, and Bioassay to Predict and Explain the Antibacterial Activity of Nonantibiotic Food and Drug Administration Drugs." Assay And Drug Development Technologies 15(3): 89-105.

11. Kruszewska, H., et al. (2002). "Search of antimicrobial activity of selected non-antibiotic drugs." Acta Poloniae Pharmaceutica 59(6): 436-439.

12. Mazumdar, K., et al. (2006). "Diclofenac in the management of E. coli urinary tract infections." In Vivo (Athens, Greece) 20(5): 613-619.

13. Mazumdar, K., et al. (2009). "The anti-inflammatory non-antibiotic helper compound diclofenac: an antibacterial drug target." European Journal Of Clinical Microbiology & Infectious Diseases: Official Publication Of The European Society Of Clinical Microbiology 28(8): 881-891.

14. Muñoz-Criado, S., et al. (1996). "In vitro activity of nonsteroidal anti-inflammatory agents, phenotiazines, and antidepressants against Brucella species." European Journal Of Clinical Microbiology & Infectious Diseases: Official Publication Of The European Society Of Clinical Microbiology 15(5): 418-420.

15. Pawar, H. V., et al. (2019). "Comparison of in vitro antibacterial activity of streptomycin-diclofenac loaded composite biomaterial dressings with commercial silver based antimicrobial wound dressings." International Journal Of Biological Macromolecules 121: 191-199.

16. Salem-Milani, A., et al. (2013). "Antibacterial Effect of Diclofenac Sodium on Enterococcus faecalis." Journal Of Dentistry (Tehran, Iran) 10(1): 16-22.

Escitalopram (n=2)

1. Cussotto, S., et al. (2019). "Differential effects of psychotropic drugs on microbiome composition and gastrointestinal function." Psychopharmacology 236(5): 1671-1685.

2. "Valipour, R., et al. (2019). ""Study of DNA-Binding Activity and Antibacterial Effect of Escitalopram Oxalate, an Extensively Prescribed Antidepressant."" Drug Research (Found to kill E.coli, but not Bacillus subtilis)

Estradiol (does not state what type of estradiol; n=1)

1. Hosoda, K., et al. (2011). "Steroid hormones as bactericidal agents to Helicobacter pylori." FEMS Microbiology Letters 318(1): 68-75.

Fluoxetine (n=6)

1. Batista de Andrade Neto, J., et al. (2019). "A mechanistic approach to the in-vitro resistance modulating effects of fluoxetine against meticillin resistant Staphylococcus aureus strains." Microbial Pathogenesis 127: 335-340

2. Brochmann, R. P., et al. (2016). "Antimicrobial synergy between carprofen and doxycycline against methicillin-resistant Staphylococcus pseudintermedius ST71." BMC Veterinary Research 12(1): 126-126.

3. Cussotto, S., et al. (2019). "Differential effects of psychotropic drugs on microbiome composition and gastrointestinal function." Psychopharmacology 236(5): 1671-1685.

4. Karine de Sousa, A., et al. (2018). "New roles of fluoxetine in pharmacology: Antibacterial effect and modulation of antibiotic activity." Microbial Pathogenesis 123: 368-371

5. Kruszewska, H., et al. (2004). "Examination of antimicrobial activity of selected non-antibiotic drugs." Acta Poloniae Pharmaceutica 61 Suppl: 18-21.

6. Munoz-Bellido, J. L., et al. (2000). "Antimicrobial activity of psychotropic drugs: selective serotonin reuptake inhibitors." International Journal Of Antimicrobial Agents 14(3): 177-180. (Review)

Flupenthixol (n=2)

1. Jeyaseeli, L., et al. (2006). "Antimicrobial potentiality of the thioxanthene flupenthixol through extensive in vitro and in vivo experiments." International Journal Of Antimicrobial Agents 27(1): 58-62.

2. Kristiansen, J. E. and B. Vergmann (1986). "The antibacterial effect of selected phenothiazines and thioxanthenes on slow-growing mycobacteria." Acta Pathologica, Microbiologica, Et Immunologica Scandinavica. Section B, Microbiology 94(6): 393-398.

Glibenclamide (n=1)

1. Koh, G. C. K. W., et al. (2013). "Glyburide reduces bacterial dissemination in a mouse model of melioidosis." Plos Neglected Tropical Diseases 7(10): e2500-e2500. (Tested against Burkholderia pseudomallei only and did not show antibacterial effect against it)

Haloperidol (n=1)

1. Mortensen, I., et al. (1992). "The antibacterial effect of some neuroleptics on strains isolated from patients with meningitis." Pharmacology & Toxicology 71(6): 449-451.

Ibuprofen (n=19)

1. Al-Janabi, A. A. H. S. (2010). "In vitro antibacterial activity of Ibuprofen and acetaminophen." Journal Of Global Infectious Diseases 2(2): 105-108

2. Cederlund, H. and P. A. Mårdh (1993). "Antimicrobial activities of N-acetylcysteine and some non-

steroidal antiinflammatory drugs." The Journal Of Antimicrobial Chemotherapy 32(6): 903-904.

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Lidocaine (n=44)

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Metformin (n=3)

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2. Kapoor, Y., et al. (2018). "Repurposing of existing drugs for the bacterial infections: An In silico and In vitro study." Infectious Disorders Drug Targets.

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Naproxen (n=2)

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Paracetamol (n=5)

1. Akhter, T., et al. (2010). "Antibacterial effect of NSAIDS on clinical isolates of urinary tract infection and diabetic foot infection." Pakistan Journal Of Pharmaceutical Sciences 23(1): 108-113.

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Propranolol (n=3)

1. Jerwood, S. and J. Cohen (2008). "Unexpected antimicrobial effect of statins." The Journal Of Antimicrobial Chemotherapy 61(2): 362-364.
2. Kapoor, Y., et al. (2018). "Repurposing of existing drugs for the bacterial infections: An In silico and In vitro study." Infectious Disorders Drug Targets.
3. Kruszewska, H., et al. (2004). "Examination of antimicrobial activity of selected non-antibiotic drugs." Acta Poloniae Pharmaceutica 61 Suppl: 18-21.

Ranitidine (n=4)

1. Alarcón, T., et al. (1999). "Bacteriostatic and bactericidal activity of ranitidine bismuth citrate in Helicobacter pylori clinical isolates." Revista Espanola De Quimioterapia: Publicacion Oficial De La Sociedad Espanola De Quimioterapia 12(1): 64-68.
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3. Hirschl, A. M., et al. (1987). "[Campylobacter pylori, gastritis and peptic ulcer]." Wiener Klinische Wochenschrift 99(14): 493-497. (Showed no antimicrobial effectiveness against H. pylori when administered alone)
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Sertraline (n=6)

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Tamoxifen (n=2)

1. El Arbi, M., et al. (2014). "Antibacterial properties and mode of action of new triaryl butene citrate compounds." European Journal Of Medicinal Chemistry 76: 408-413. (Tested Tamoxifen analogues rather than Tamoxifen itself. Analogues showed antimicrobial properties)
2. Montoya, M. C. and D. J. Krysan (2018). "Repurposing Estrogen Receptor Antagonists for the Treatment of Infectious Disease." Mbio 9(6). (review)

Tramadol (n=3)

1. Farzam, H., et al. (2018). "Antibacterial effect of tramadol against Staphylococcus aureus and Pseudomonas aeruginosa: an in vivo study." New Microbes And New Infections 24: 42-46. (No antimicrobial effect)
2. Kruszewska, H., et al. (2002). "Search of antimicrobial activity of selected non-antibiotic drugs." Acta Poloniae Pharmaceutica 59(6): 436-439.
3. Tamanai-Shacoori, Z., et al. (2007). "The antibacterial activity of tramadol against bacteria associated with infectious complications after local or regional anesthesia." Anesthesia And Analgesia 105(2): 524-527.

Venlafaxine (n=1)

1. Kavitha, C. V., et al. (2006). "Synthesis of new bioactive venlafaxine analogs: novel thiazolidin-4-ones as antimicrobials." Bioorganic & Medicinal Chemistry 14(7): 2290-2299. (Tested Venlafaxine analogues rather than Venlafaxine itself. Analogues showed antimicrobial properties)

No relevant records were identified for the following drugs: Atenolol, Bezafibrate, Carbamazepine, Citalopram, Dextropropoxyphene, Diazepam, Estradiol (E2), Estriol (E3), Estrone (E1), Ethinylestradiol (EE2), Felodipine, Ifosfamide, iodine-123, Iodine-125, Iodine-129, Iodine-131, Irbesartan, Levonorgestrel, Meclozine, Mefanamic acid, Oxazepam, Risperidone

Appendix IX Consideration of confidence in PNEC values

Introduction

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

$$RQ = \frac{PEC}{PNEC}$$

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

$$RQ = \frac{MEC}{PNEC}$$

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

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

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

Evaluating the environmental response or effect is done via determining the PNEC, which is defined as the concentration below which effects are not expected to occur. Although PNECs can be derived for a range of habits or fauna, unless specified otherwise usually $PNEC_{fresh\ water}$ is implied.

PNECs are based on laboratory-based ecotoxicity experiments for a range of endpoints, whereby a single species is exposed to a single drug. Most commonly, endpoints include growth, reproduction or mortality. Data are typically reported as the concentrations where either a percentage reduction of the parameter was observed, typically either 50% inhibition of growth or mortality (EC50 or LC50; Median Effective Concentration/ Median Lethal Concentration), or – preferably - as No Observed Effect Concentration (NOEC), where NOEC is the highest concentration tested with no statistical significant difference in effect compared to the control. In preference, values should be obtained from long-term (chronic) eco-toxicity studies, which extend over multiple generations of the test organism. The accepted base-set of organisms for deriving $PNEC_{fresh\ water}$ comprises of algae, *Daphnia* and fish, representing three trophic levels: algae as primary producers; *Daphnia* as primary consumers and fish as secondary consumers (European Chemicals Agency, 2008). The result from the most sensitive species being used in the risk evaluation.

To calculate the PNEC, an Assessment Factor is then applied, which can range from 10 to 1000. This is included as a protective factor to allow the transfer of laboratory results to real ecosystems, for the fact that the laboratory evaluation does not include the entire range of organisms present in these situations and for the fact that other stressors will be present. The more extensive the experimental ecotoxicity data available, the smaller the Assessment Factor (Table 1).

Table 1: Assessment factors used to derive a $PNEC_{fresh\ water}$ (European Chemicals Agency, 2008)	
Available data	**Assessment factor**
At least one short-term L(E)C_{50} from each of three trophic levels (fish, Daphnia and algae)	1000
One long-term EC_{10} or NOEC (either fish or Daphnia)	100
Two long-term results (e.g. EC_{10} or NOECs) from two trophic levels (fish and/or Daphnia and/or algae)	50
Long-term results (e.g. EC_{10} or NOECs) from the three species (normally fish, Daphnia and algae) representing three trophic levels	10

Quality assurance issues associated with PNEC data

Given that the eco-toxicological parameter from the most sensitive species is used in the risk assessment or even, in the case of multiple NOEC's or EC_{50}'s, the lowest value (relating to the most sensitive end point) from one species, ensuring that the data is adequate is paramount. Adequacy, as defined in the European Chemicals Agency's Technical Guidance Document on Risk Assessment, has two elements:

- reliability: covering the inherent quality of a test relating to test methodology and the way that the performance and results of the test are described;
- relevance: covering the extent to which a test is appropriate for a particular hazard or risk assessment.

Relevance refers, *inter alia*, to appropriate end points and test conditions. Traditionally, reliability has been assessed using the Klimisch scoring approach (Klimisch et al., 1997), which rates PNEC data as K1: reliable without restrictions; K2: reliable with restrictions; K3: unreliable or K4: not assignable (Table 2). Generally only PNEC generated from work rated as K1 or K2 should be considered.

More recently, the society of Environmental Toxicology and Chemistry project "*Criteria for Reporting and Evaluating Ecotoxicity Data (CRED)*" involving 75 risk assessors from 12 countries (Kase et al., 2016) produced a more detailed evaluation method. The Klimisch et al. (1997) has, 14 evaluation criteria/questions for chronic ecotoxicity (12 for acute ecotoxicity) that should be met to enable confidence in the reliability of the data, whereas CRED has a set of 20 reliability and 13 relevance criteria (Moermond et al., 2016). Where the reliability criteria refer to the laboratory testing procedure, analysis and the relevance criteria cover wider aspects such as "Is the species tested relevant for the compartment under evaluation?" For example, earthworm data would not be relevant if the study were considering freshwater exposure. Additionally, the CRED protocol recommends 50 reporting criteria for publications purporting to establish PNEC data to enable data published to reliably be used as secondary information. Similar to the Klimisch et al. (1997), the CRED evaluation method establishes four reliability categories: reliable without restrictions (R1), reliable with restrictions (R2), not reliable (R3), and not assignable (R4).

The CRED protocol seems to be a following on or development of the work by Ågerstrand et al., (2011) identifying evaluation criteria regarding the use of ecotoxicity data for environmental risk assessment of pharmaceuticals. These authors identified 44 mandatory criteria and 19 optional criteria required for the reliability evaluation.

Additionally, the European Medicines Agency (EMA) requires all newly marketed human pharmaceuticals should have an environmental risk assessment (ERA), experimental studies to produce the PNEC should

Table 2 Summary of the Klimisch Criteria (Benson et al., 2017)		
Code	**Category**	**Description**
1	Reliable without restrictions	Refers to studies/data carried out or generated according to internationally accepted testing-guidelines (preferably good laboratory practice {GLP}) or in which the test parameters documented are based on a specific (national) testing guideline (preferably GLP), or in which all parameters described are closely related/comparable to a guideline method.
2	Reliable with restrictions	Studies or data (mostly not performed according to GLP) in which the test parameters documented do not comply totally with the specific testing guideline, but are sufficient to accept the data or in which investigations are described that cannot be subsumed under a testing guideline, but which are nevertheless well-documented and scientifically acceptable.
3	Not reliable	Studies/data in which there are interferences between the measuring system and the test substance, or in which organisms/test systems were used that are not relevant in relation to exposure, or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for an assessment and which is not convincing for an expert assessment.
4	Not assignable	Studies or data which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature.

preferably follow standard test protocols produced by, for example, by OECD (Organisation for Economic Cooperation and Development), AFNOR (Association Française de Normalisation) or ISO (International Organization for Standardization) and be conducted in compliance with Good Laboratory Practices (GLP) (EMA, 2006). However, there was no backdating of this requirement and many pharmaceuticals, even the ubiquitous ones such as ibuprofen or amoxicillin do not have an ERA. Burns et al. (2018) reported that only 71 of the top 350 pharmaceuticals in use in the UK had environmental risk assessment (ERA) available via the EMA European Medicines Agency as European Public Assessment Reports and of those registered for market use in the UK (1912 pharmaceuticals) only around 11% had ERA's.

Klimisch et al. (1997); EMA (2006) and CRED recommend the adoption of GLP and all studies identifying evaluation criteria base their evaluation on standard test protocols. All allow non-standard protocols to be used a large number of the evaluation criteria would be met if PNEC evaluations are preformed following these standard protocols.

Reliability evaluation of PNEC data

Since scientific journals tend to emphasize conciseness it is difficult for enough information to be presented for the evaluation protocols to rate the study reliable without restrictions, reliable with restrictions, etc. Therefore, these are often overlooked and the emphasis placed on commissioned studies either for submission to regulators or as evidence requested by governmental bodies such as the WFD.

Some, such as the eChemPortal (Global Portal to Information on Chemical Substances) (https://www.echemportal.org/echemportal/propertysearch/page.action?pageID=0) operated by OECD have a database of ecotoxicological information which are categorised into the reliability categories, presumably based on Klimisch et al. (1997) scoring system, however this database appear to focus on organic chemicals and to a lesser degree metal salts. There does not appear to be a database which offers a similar evaluation for pharmaceuticals.

Fass.se (https://www.fass.se/LIF/startpage?userType=0) does quote data, often from pharmaceuticals companies, which are presumably reliable. Additionally, a number of papers have been published written exclusively or mainly by employees of pharmaceuticals companies (Caldwell et al., 2012; Murray-Smith et al., 2012; Vestel et al., 2016 and Tell et al., 2019). The PNEC published in these manuscripts are likely to be drawn from the respective companies' database and thus can be considered as reliable, although there is a lack of transparency on underlying ecotoxicity studies. Table 3 provides a comparison of the PNEC data obtained as part of the literature review of this CREW study and those for the comparable pharmaceuticals from papers published by the pharmaceutical industries. It is clear that the greatest discrepancy occurs when the lowest PNEC found for the selected pharmaceuticals in this project was obtained from published papers, for example for trimethoprim, the PNEC adopted in this project was obtained from Orias and Perrodin (2013) at 0.0058 µg/L but that from the pharmaceutical industries was 100 µg/L. Orias and Perrodin (2013) quoted work using freshwater zebra mussels, which based on their assessment was the most sensitive of the 20 species examined and the endpoint was decreased metabolic activity. Thus, these authors looked at a more sensitive endpoint than inhibition of growth or death.

The above highlights another important point: while the information obtained from the papers produced by representatives of the pharmaceutical industry will focus on the three baseline set of organisms: algae, *Daphnia* and fish and report on standard endpoints (i.e. death or growth inhibition), data from published papers reporting on academic studies can report on non-standard test organisms and endpoints. This information is acceptable as long as the study met the criteria of reliability.

Without reviewing the original data sources cited in the "CREW all data 16 Dec" spreadsheet using either Klimisch et al. (1997) or Moermond et al. (2016) approach, probably only those PNEC that were obtained from work associated with the Water Framework Directive should be thought as reliable enough to be used in creating a priority list of pharmaceuticals to be used in Scotland although PNEC data submitted to Fass.se is thought to be subject to some scrutiny and may be sufficiently reliable.

Table 3: PNEC values for selected compounds

Compound	CREW database (µg/L)	Reference (taken from the CREW all data spreadsheet)	Pharma papers (µg/L)	Reference
17-alpha ethinyl oestradiol (EE2)	0.000035	WFD EQS Dossier	0.0001	Caldwell et al. 2012
17-beta oestradiol (E2)	0.0004	WFD EQS Dossier	0.002	Caldwell et al. 2012
Atenolol	148	NCIP 2015-2020	148	Vestel et al. 2016
Atorvastatin	1.7	NCIP 2015-2020	14	Vestel et al. 2016
Azithromycin	0.019	Loos et al. 2018	0.02	Tell et al. 2019
Bezafibrate	50	Boillot, 2008	1000	Vestel et al. 2016
Ciprofloxacin	0.089	NCIP 2015-2020	0.57	Tell et al. 2019
Clarithromycin	0.12	Loos et al. 2018	0.08	Tell et al. 2019
Erythromycin	0.2	Loos et al. 2018	0.5	Tell et al. 2019
Estriol (E3)	0.06	Caldwell et al. 2012	0.06	Caldwell et al. 2012
Ibuprofen	0.01	NCIP 2015-2020	1	Johnson & Johnson
Irbesartan	704	FASS Allmänhet. 2013	704	Vestel et al. 2016
Lidocaine	32	FASS Allmänhet. 2013	110*	Murray-Smith et al. 2011
Metformin	13.45	NCIP 2015-2020	1030	Vestel et al. 2016
Naproxen	0.64	Grung et al. 2007	4.2	Murray-Smith et al. 2011
Oestrone (E1)	0.0036	Loos et al. 2018	0.006	Caldwell et al. 2012
Oxytetracycline	18	Tell et al., 2019	18	Tell et al. 2019
Propranolol	0.1	NCIP 2015-2020	0.02	Vestel et al. 2016
Sulfamethoxazole	0.59	Ferrari et al. 2004	0.6	Tell et al. 2019
Tamoxifen	0.49	NCIP 2015-2020	0.49**	Vestel et al. 2016
Tramadol	64	Webb 2000	73	Vestel et al. 2016
Trimethoprim	0.0058	Orias and Perrodin 2013	100	Tell et al. 2019

NCIP 2015-2020: The National Chemical Investigations Programme 2015-2020

Johnson & Johnson: Information obtained from https://www.nsfwetcenter.org/2018/09/11/new-pnec-list-9-11-18/ citing data from Johnson & Johnson

* listed as lidocaine hydrochloride

** listed as tamoxifen citrate

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Appendix X Overview of all studies

Colour coding : Green indicates datasets that were used in the analysis, blue indicated datasets that were sought but not received, and grey indicates datasets that were not suitable for use (too old/predicted not measured).

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
1	Letsinger, P. Kay, S. Rodríguez-Mozaz, et al., Spatial and temporal occurrence of pharmaceuticals in UK estuaries, Science of the Total Environment, https://doi.org/10.1016/j.scitotenv.2019	Peer-reviewed article	S. Letsinger, P. Kay, S. Rodríguez-Mozaz, et al., Spatial and temporal occurrence of pharmaceuticals in UK estuaries, Science of the Total Environment, https://doi.org/10.1016/j.scitotenv.2019.04.182	Ibuprofen, citalopram, diclofenac, paracetamol, trimethoprim	Cromarty, Forth and Tay estuaries	2014	Corresponding author: p.kay@leeds.ac.uk	Included
2	CIP2	Industry report		10,11-epoxy-Carbamazepine, 17-alpha ethinyloestradiol (EE2), 17-beta oestradiol (E2), atenolol, atorvastatin, azithromycin, carbamazepine, ciprofloxacin, clarithromycin, diclofenac, erythromycin, fluoxetine, ibuprofen, metformin, norerythromycin, norsertraline, oestrone (E1), ortho-Hydroxyatorvastatin, para-Hydroxyatorvastatin, propranolol, ranitidine, sertraline, tamoxifen, triclosan	WWTP influents, effluents; rivers up and downstream from WWTP.	2015-2017	A range of non-pharmaceutical compounds was also analysed.	Included
3	Zhang et al (2017)	Peer-reviewed article	Zhang et al (2017) Risk estimation and annual fluxes of emerging contaminants from a Scottish priority catchment to the estuary and North Sea. Environmental Geochemistry and Health: 1-19.	Diclofenac, ibuprofen, paracetamol, tramadol, carbamazepine, triclosan, estrone, 17Beta-estradiol, estriol	Surface water (River Ugie)		Also tested for BPA, comparison of spot and passive sampling in catchment, analysis of temporal and spatial trends of compounds in river over 12 months, Ibuprofen and carbamazepine most abundant pharma. Risk assessment found BPA had highest risk.	Included
5	Niemi PhD	PhD Research	L. Niemi, S. Gibb, M. Taggart, K. Boyd, Z. Zhang, Caithness General Hospital (Wick) Wastewater Project (unpublished)	17-alpha-Ethinylestradiol, carbamazepine, clarithromycin, diclofenac, fluoxetine, ibuprofen, paracetamol, trimethoprim	Hospital wastewater	2018		included

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
6	SEPA Watch List Monitoring	Regulatory monitoring		Wide range of compounds. Data included for 10,11 hydroxy carbazepine, 17 alpha ethinyl oestradiol, 17 beta oestradiol, amitriptyline, atenolol, azithromycin, bezoylecgonine, bezafibrate, caffeine, carbamazepine, ciprofloxacin, citalopram, clarithromycin, clopidogrel, cocaine, diazepam, diclofenac, erythromycin, fluoxetine, gabapentin, gliclazide, ibuprofen, iohexol, irbesartan, lidocaine, lorazepam, losartan, metformin, naproxen, oestrone, oxazepam, paracetamol, propranolol, ranitidine, sertraline, sulfamethoxazole, tramadol, triclosan, trimethoprim, venlafaxine	Mainly rivers	ongoing		included
7	Niemi PhD	PhD Research	L. Niemi, S. Gibb, M. Taggart, K. Boyd, Z. Zhang, River Dee pharmaceutical monitoring (unpublished)	17-alpha-Ethinylestradiol, carbamazepine, clarithromycin, diclofenac, fluoxetine, ibuprofen, paracetamol, trimethoprim	River Dee	2019		included
8	Niemi PhD	PhD Research	L. Niemi, S. Gibb, M. Taggart, K. Boyd, Z. Zhang, Pharmaceutical monitoring within the wastewater treatment process (unpublished)	17-alpha-Ethinylestradiol, carbamazepine, clarithromycin, diclofenac, fluoxetine, ibuprofen, paracetamol, trimethoprim	Wastewater processes	2018		included
9	Ramage et al. (2018)	Peer-reviewed article	S. Ramage, D. Camacho-Muñoz & B. Petrie, Enantioselective LC-MS/MS for anthropogenic markers of septic tank discharge, Chemosphere, https://doi.org/10.1016/j.chemosphere.2018.12.007	R(-)-Amphetamine, caffeine, carbamazepine, carbamazepine 10,11 epoxide, cotinine, paracetamol, R(+)-Atenolol, S(_)-Atenolol, R(-)-Chlorpheniramine, (S+)-Chlorpheniramine, (R-)-Citalopram, (S+)-Citalopram, (R-)-Fluoxetine, S(+)-Fluoxetine, Methylparaben, R(+)-propranolol, S(-)-propranolol, salbutamol enantiomer 1, salbutamol enantiomer 2.	Surface water and septic tank effluent.	2018		included

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
10	Pahl, O (Project Lead) & Helwig, K (Lead author, corresponding author). noPILLS in Waters: noPILLS report: Interreg IV B NWE project partnership (2015)	EU Research Project	Pharmaceuticals in sewage systems and surface waters - status quo (Chapter 3). Helwig, K (lead author, corresponding author). noPILLS in Waters: noPILLS report: Interreg IV B NWE project partnership (2015). Essen: Emschergenossenschaft, 24 - 41.	Report: Sulfamethoxazole, naproxen, ibuprofen, erythromycin, diclofenac, clarithromycin, ciprofloxacin, carbamazepine, atenolol, cyclophosphamide, lidocaine, bezafibrate. Raw data: 4-hydroxydiclofenac, amphetamine, atenolol, benzoylecgonine, bezafibrate, caffeine, carbamazepine, ciprofloxacin, citalopram, clarithromycin, cyclophosphamide, diclofenac, erythromycin, fluoxetine, ibuprofen, ifosfamide, iohexol, lidocaine, n-acetyl sulfamethoxazole, oxytetracycline, paracetamol, paroxetine, propranolol, ranitidine, sulfamethoxazole.	WWTP influent and effluent (2 WWTPs in Scotland), surface water upstream and downstream of WWTP, surface water (River Almond)	2014-15	Comparison of WWTPs with conventional activated sludge and trickling filter technologies (monitoring in Germany, Luxembourg, France), removal efficiencies calculated and observed carbamazepine, clarithromycin and lidocaine persistent across all study sites. Several antibiotics observed in surface waters at toxicologically relevent concentrations. Sludge from hospital wastewater also investigated (propranolol, ketoprofen, econazole, salicyclic acid). Ferrate removal of pharma in secondary wastewater (Glasgow) also investigated to validate lab studies.	Scottish data included
11	P. Landova, S. Gibb, M. Taggart, Pharmaceutical monitoring in the River Thurso (Caithness)	PhD research	P. Landova, S. Gibb, M. Taggart, Pharmaceutical monitoring in the River Thurso (Caithness)	17 alpha ethinyloestradiol,carbamazepine, clarithromycin, diclofenac, fluoxetine, ibuprofen, paracetamol, trimethoprim.	WWTP and rivers	2018		included

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
	Loos, R., Marinov, D., Sanseverina, I., Napierska, D., Lettieri, T	Regulatory report	Review of the first Watch List under the Water Framework Directive and recommendations for the second Watch List. Loos, R., Marinov, D., Sanseverina, I., Napierska, D., Lettieri, T. (2018). JRC Technical Reports	17-alpha-ethynylestradiol (EE2), estrone (E1), 17-beta-estradiol (E2), diclofenac, 2,6-di-tert-butyl-4-methylphenol, erythromycin, clarithromycin, azithromycin	Surface water in 25 EU Member States		Environmental risk determined for target compounds based on monitoring data carried out every 2 years, and whether Environmental Quality Standards should be set at the EU level. Compounds added and taken from list based on risk/monitoring data. This report presents data gathered during 1st Watch List monitoring campaign (2015), found EE2, imidacloprid, E2, diclofenac, estrone, clarithromycin and azithromycin exceeded PNEC in surface water across EU. Pesticides oxadiazon, methiocarb, tri-allate and insecticides imidacloprid, thiacloprid, thiamethoxam, clothianidin, acetamiprid and personal care product 2-ethylhexyl 4-methoxycinnamate included on list. It determined that diclofenac, 2,6-di-tert-butyl-4-methylphenol, tri-allate and 2-ethylhexyl-4-methoxycinnamate should be removed from Watch List 2 (2018). Potential inclusion of venlafaxine, proquinazid, amoxicillin, ciprofloxacin, metconazole, famoxadone on 3Watch List.	No response from author

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
	Kargar, Kiana (2017)	PhD Thesis	Analytical studies of amoxicillin and erythromycin by LC-MS/MS in environmental and waste waters in Central Scotland. Kargar, Kiana (2017). Glasgow Caledonian University.	Amoxicillin, erythromycin (and degradation products)	WWTP influent, effluent (Fauldhouse and Harthill, Edinburgh), surface water (River Almond) and campus wastewater (GCU Health and Engineering buildings)	2014/15	Sample prep and LC-MS/MS analysis method validation in wastewaters. Appreciable removal of amoxicillin during WWT observed, erythromycin effluent concentrations higher than influent and degradation products detected downstream WWTP, 24 hour sampling regimes give daily concentrations of compounds entering and leaving WWTPs, 7 sites along River Almond were sampled over 4 consecutive days and results show initial pharma temporal and spatial trends	Data requested but not received
	Langford et al (2011)	Peer-reviewed article	Multi-residue screening of prioritised human pharmaceuticals, illicit drugs and bactericides in sediments and sludge. Langford et al (2011). Journal of Environmental Monitoring 13: 2284-2291.	Atenolol, carbamazepine and citalopram, triclosan and triclocarban	Scottish sewage sludge and freshwater sediments	<2011	Also tested for illicit drugs, but were not detected in any of the samples	data too old
	Loos et al (2008)	Regulatory monitoring	EU wide monitoring survey of polar persistent pollutants in European river waters. Loos et al (2008). JRC Scientific and Technical Reports 48459.	Bezafibrate, carbamazepine, diclofenac, estrone, gemfibrozil, ibuprofen, ketoprofen, naproxen, sulfamethoxazole	Surface water (Rivers Forth and Clyde)	<2009	Also tested for perfluorinated chemicals, pesticides, benzotriazoles, alkylphenols (35 compounds total) in 122 EU rivers	data too old
	Nebot et al (2007)	Peer-reviewed article	Quantification of human pharmaceuticals in water samples by high performance liquid chromatography-tandem mass spectrometry. Nebot et al (2007). Analytica Chimica Acta 598: 87-94.	Mefenamic acid, ibuprofen, erythromycin, paracetamol, trimethoprim, sulfamethoxazole, propranolol, dextropropoxyphene, tamoxifen, lofepramine, diclofenac, clofibric acid	WWTP effluent (Caithness)	<2007	Also monitored sea water, river water and tap water but no pharma detected	data too old

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
	Nebot et al (2015)	Peer-reviewed article	Introduction of human pharmaceuticals from wastewater treatment plants into the aquatic environment: a rural perspective. Nebot et al (2015). Environmental Science and Pollution Research 22: 10559-10568.	Diclofenac, mefenamic acid, ibuprofen, propranolol, paracetamol, tamoxifen, trimethoprim, erythromycin, dextropropoxyphene, sulfamethoxazole	WWTP effluent, surface water (Thurso)	Sampling <2014	Also tested for clofibric acid (not detected), temporal trends in River Thurso were investigated with 4 sampling sites ranging above WWTP outflow to harbour	Data too old
	Gardner et al (2012)	Peer-reviewed article	The significance of hazardous chemicals in wastewater treatment works effluents. Gardner et al (2012). Science of the Total Environment 437: 363-372.	17-alpha-Ethinylestradiol, 17-beta-estradiol, diclofenac, erythromycin, estrone, fluoxetine, ibuprofen, ofloxacin, oxytetracycline, propranolol, salicyclic acid, triclosan	WWTP effluent (15 WWTPs in Scotland)	2011?	Also tested for polycyclic aromatic hydrocarbons, metals and penta-congeners (70 compounds total), study monitored 162 WWTPs in UK. Erythromycin, triclosan, oxytetracycline, ibuprofen, propranolol, fluoxetine, diclofenac 17beta-estradiol and 17alpha-ethinylestradiol detected above EQS in final effluents of >50% WWTPs. CIP 1.	Data too old
	Gardner et al. (2013)	Peer-reviewed article	Performance of UK wastewater treatment works with respect to trace contaminants. Gardner et al. (2013). Science of the Total Environment 456-457: 359-369.	17-alpha-Ethinylestradiol, 17-beta-estradiol, diclofenac, erythromycin, estrone, fluoxetine, ibuprofen, ofloxacin, oxytetracycline, propranolol, salicyclic acid, triclosan	WWTP influent, settled sewage, final effluent and sludge (15 WWTPs in UK)	2011?	Influent-effluent removal efficiencies determined for pharmaceuticals and other organic pollutants, where available secondary sewage samples were collected (tertiary treatment), large range of removals observed (21-99%), no information given on number or location of Scottish WWTPs	Data too old
	Jones et al (2014)	Peer-reviewed article	Concentrations of trace substances in sewage sludge from 28 wastewater treatment works in the UK. Jones et al (2014). Chemosphere 111: 478-484.	Diclofenac, ibuprofen, propranolol, erythromycin, ofloxacin, oxytetracycline, fluoxetine	Sewage sludge (28 WWTPs in UK)	(CIP1 - sampling <2014)	Tested for metals, polycyclic aromatic hydrocarbons and other organic pollutants (40 compounds total), no information given on number or location of Scottish WWTPs, observed concentrations generally below sewage sludge directive standards and risk to soil low (from PNEC)	Data too old

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
	Jiang et al (2013)	Peer-reviewed article	Pharmaceutical removal from wastewater by ferrate (VI) and preliminary effluent toxicity assessments by the zebrafish embryo model. Jiang et al (2013). Microchemical Journal 110: 239-245.	Ciprofloxacin, sulfamethoxazole, erythromycin, naproxen, ibuprofen, atenolol, cyclophosphamide, ifosfamide, carbamazepine, bezafibrate, lidocaine	Secondary effluent (Shiedhall WWTP, Glasgow)	<2013	Raw samples were analysed for pharmaceuticals, and then spiked for batch experiments Ferrate (VI) removal, also tested for one human metabolite (n-acetyl sulfamethoxazole), further information in PhD thesis 'Removal of pharmaceutical from water and wastewater by Ferrate (VI)', 2013 Glasgow Caledonian University.	Data too old
	Zhou, Zhengwei (2013)	PhD Thesis	Removal of pharmaceutical from water and wastewater by Ferrate (VI). Zhou, Zhengwei (2013). Glasgow Caledonian University.	Ciprofloxacin, sulfamethoxazole, erythromycin, naproxen, ibuprofen, atenolol, cyclophosphamide, ifosfamide, carbamazepine, bezafibrate, lidocaine	Secondary effluent (Shiedhall WWTP, Glasgow)	<2013	Removal of pharma from wastewater using Ferrate (VI) investigated, real water samples collected and analysed for pharma concentrations, batch experiments to determine optimal conditions and removal rates with ferrate (VI) and identify transformation products	Data too old
	Fernand, Rosemary A. (2009)	PhD Thesis	The fate and effects of healthcare waste produced by the National Health Service in Scotland: with a focus on pharmaceuticals. Fernand, Rosemary A. (2009). Glasgow Caledonian University.	Sulfamethoxazole, acetyl-sulfamethoxazole, clofibric acid, dextropropoxyphene, diclofenac, erythromycin, ibuprofen, mefenamic acid, paracetamol, propranolol, tamoxifen, trimethoprim, atenolol, bendroflumethiazide, clotrimazole, salicyclic acid	WWTP influent, effluent, activated sludge and final sludge (Dalmuir and Shiedhall, Glasgow), surface water (River Clyde), municipal solid waste (Dunoon and Levenseat treatment plants)	<2009	Mixed pharma detected in final effluent and activated sludge, as well as final solid product mixed with municipal (i.e. household) waste that is directly applied to soil. Mass balance of pharma in Shiedhall WWTP calculated, and risk assessment performed - most pharma RQ<1 in wastewater, and diclofenac, paracetamol, aclicyclic acid and ibuprofen MEC exceeded EU limits in solid waste applied to land	Data too old

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
	Roberts, Joanne B	PhD Thesis	Determination and identification of drug and chemical metabolites in wastewater by LCMSMS. Roberts, Joanne B. (2017). Glasgow Caledonian University	Simvastatin, omeprazole, carbamazepine	Wastewater influent and effluent, Hospital and care facility wastewater (WWTP and hospital not identified)	<2012	Identification of abundant metabolites/degradates and reported removal during WWT, most poorly removed (omeprazole, omeprazole degradation product, simvastatin metabolite and carbamazepine + metabolites). Effluent concentrations of carbamazepine higher than influent. Use of PILLS target list (and data) for analysis of prescribing rates and drug loads 2011 - 2015. Increase in cabamazepine replacement drugs (oxcarbazepine, eslicarbazepine) reported.	Data too old
	Al Qarni, Hamed M. (2015)	PhD Thesis	Investigating human pharmaceutical compounds present in municipal and hospital wastewater and options for their removal. Al Qarni, Hamed M. (2015). Abertay University.	Paracetamol, naproxen, ibuprofen, carbamazepine, stenolol, benzafibrate, lidocaine, ciprofloxacin, clarithromycin, sulfamethoxazole, cyclophospham, ifosfamide	Hospital wastewater, WWTP influent and effluent (4 WWTPs in Fife and Tayside)	2013	WWTP influent-effluent removal efficiencies determined, optimum WWTP working parameters in secondary biological treatment investigated, comparison of hospital wastewater in UK and Saudi Arabia for on-site hospital wastewater treatment, 1 published article found (focus Saudi Arabia hospitals)	data too old
	Helwig, Karin P.M. (2015)		Pharmaceutical residues in the aquatic environment in Scotland: Sources, occurrence and environmental risk. Helwig, Karin P.M. (2015). Glasgow Caledonian University.	Atenolol, ciprofloxacin, lidocaine, carbamazepine, naproxen, bezafibrate, sulfamethoxazole, clarithromycin, cyclophosphamde, ifosfamide, iopamidol, iopromide, diatrizoate	Hospital wastewaters and WWTP influent from rural and urban area Scotland	2011	Effluents from two different sites of rural hospital + rural's municipal wastewater (minus hospital contribution) and discharges from 2 different sites of urban hospital and urban WWTP influent sampled for selected pharmaceuticals	Data too old

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
		Research project report	Pharmaceutical input and elimination from local sources: Final report of the European cooperation project PILLS. Lyko, S. Nafo, I., Herman, E., Benetto, E., Cornelissen, A., Igos, E., Klepiszewski, K., Venditti, S., Kovalova, L., McArdell, C., Helwig, K., Hunter, C., Jiang, J., MacLachlan, J., McNaughtan, M., Pahl, O., Roberts, J., Barraud, O., Casellas, M., Dagot, C., Maftah, C., Ploy, M-C., Stalder, T. (2012). Essen: Emschergenossenschaft, 150.	Atenolol, carbamazepine, diclofenac, naproxen, lidocaine, ifosfamide, cyclophosphamide, ciprofloxacin, erythromycin, clarithromycin, sulfamethoxazole, n-acetyl-sulfamethoxazole, iopromide, iopamidol, diatrizoate, bezafibrate	Hospital wastewater (3 hospitals and 1 geriartric ward in Scottish Borders and Glasgow)	2011	Comparison of UK hospital wastewater in Scotland to several European countries, with and without on-site treatment. Determined that advanced tertiary treatment required for hospital wastewaters to prevent risk to effluent-receiving environment, however formation of chemical degradation products largely unknown. Discussion of antibiotic resistant bacteria in hospital wastewater and removal during WWTP	Data too old
	Helwig, K et al (2013)	Peer-reviewed article	Micropollutant Point Sources in the Built Environment: Identification and Monitoring of Priority Pharmaceutical Substances in Hospital Effluents. Helwig, K et al (2013). Environmental and Analytical Toxicology 3:4.	Atenolol, carbamazepine, diclofenac, naproxen, lidocaine, ifosfamide, cyclophosphamide, ciprofloxacin, erythromycin, clarithromycin, sulfamethoxazole, n-acetyl-sulfamethoxazole, iopromide, iopamidol, diatrizoate, bezafibrate	Hospital wastewater (3 hospitals and 1 geriartric ward in Scottish Borders and Glasgow)		Comparison of hospital wastewater across 6 countries (8 hospitals total), found that hospitals are an important source of some pharmaceuticals (i.e. contrast agents and antibiotics) but not all. Publication of PILLS findings (previously listed citation)	Data too old
	Helwig, K et al (2016)	Peer-reviewed article	Ranking prescribed pharmaceuticals in terms of environmental risk: Inclusion of hospital data and the importance of regular review. Helwig, K et al (2016). Environmental Toxicology and Chemistry 35: 4 1043 - 1050.	Amoxicillin, piperacillin, flucloxacillin, penicillin, tazobactam, erythromycin, ketoconazole, ciprofloxacin, oxytetracycline, propranolol, clotrimazole, naproxen, amlodipine, venlafaxine, metformin, ethynylestradiol, povidone-iodine, ferrous sulphate, allopurinol, fluoxetine, clopidogrel, clarithromycin, gentamicin, carbamazepine, ezetimibe, ranitidine	Scottish hospitals (no environmental monitoring)	n/a	Environmental risk assessment on select pharma originating in hospital wastewaters in UK (Scotland). Based on consumption in hospitals (not only community prescribing). No environmental monitoring data, risk assessment based on pharma use in Scottish hospitals. Overall, antibiotics found to have the highest risk.	Predicted values only

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
	Zhang et al (2011)	Peer-reviewed article	Selective pressurized liquid extraction of estrogenic compounds in soil and analysis by gas chromatography–mass spectrometry. Zhang et al (2011). Analytica Chimica Acta 24(1): 29-35.	Four estrogens: estrone (E1), 17-beta-estradiol (E2), 17-alpha-ethynylestradiol (EE2), estriol (E3)	Soil samples (8 sites) from Hartwood, Northeast Scotland	<2011	SPLE and GC-MS methods validated for extraction of the selected endocrine disrupting chemicals using spiked soil samples after which methods were applied successfully to extract and detect target estrogenic compounds in soil samples collected from Northeast Scotland.	Data too old
	Thomas, K., Reid, M., Langford, K., Ridgeway, I. (2010)	Peer-reviewed article	Methodology for the analysis of selected pharmaceuticals and drugs of abuse in sediments and sludge (SNIFFER ER09 Final report). Thomas, K., Reid, M., Langford, K., Ridgeway, I. (2010). SNIFFER: Scotland, UK.	Amoxicillin, amphetamine, atenolol, carbamazepine, ,cocaine, benzoylecgonine, codeine, ciprofloxacin, citalopram, diclofenac, fluoxetine, ibuprofen, levothyroxine sodium, methamphetamine, salbutamol, simvastatin, triclocarban, triclosan	Sewage sludge (3 Scottish WWTPs - 1 in Western Scotland, 1 in Central and 1 in Eastern), sediment samples from upstream and downstream 3 WWTPs	<2010	No effluent or surface water data - pharma and drugs of abuse method development study in Scottish sediment and sludge. WWTPs selected based on population size and hospital input. In-depth pharma selection process (included in report). Final results show that method is suitable for selected compounds (with good recoveries, %RSDs and LODs). Triclosan and triclocarban detected in highest concentrations in samples, detected all samples. Atenolol, citalopram, carbamazepine and ibuprofen also detected in samples, no illicit drugs detected. Low sample numbers collected so no analysis on frequency/ concentration of target pharma detected in Scottish environment.	data too old

Ref. no. in database	Project, programme or study	Study type	Citation	Pharmaceutical compounds	Samples and Study site(s)	Sampling year or period	Notes	Included or reason for exclusion
	Negrao De Carvalho, R., Ceriani, L., Ippolito, A., Lettieri, T. (2015)	Regulatory report	Development of the First Watch List under the Environmental Quality Standards Directive. Negrao De Carvalho, R., Ceriani, L., Ippolito, A., Lettieri, T. (2015). JRC Technical Reports.	Diclofenac, 17-alpha-ethynylestradiol (EE2), 17-abeta-estradiol (E2), 2,6-ditert-butyl-4-methylphenol, erythromycin, clarithromycin, azithromycin	No environmental data - predicted environmental concentrations included	n/a	Report to identify a list of substances for inclusion on the Watch List monitoring carried out in EU member states (under Water Framework Directive). Ranking of substances based on proposal by member states, flagged in literature, PEC calculation (from physicochemical properties, usage, etc), PNEC calculation (from ecotox data) for final risk characterisaiton. Pesticides oxadiazon, methiocarb, tri-allate and inseciticides imidacloprid, thiacloprid, thiamethoxam, clothianidin, acetamiprid and personal care product 2-ethylhexyl 4-methoxycinnamate included on list.	Predicted values only
	Environmental Protection Agency, Scottish Pollutant Release Inventory (online dataset)		Scottish Environmental Protection Agency, Scottish Pollutant Release Inventory (online dataset)	X-ray contrast media (iodine-123, -225, -129, -131), clotrimazole, triclosan	WWTP effluents in Scotland	2015-2019	Database is publicly available for download, spans 2002 - 2018 with annual mass releases of target compounds. Includes PAHs, PBDEs, halogenated organic compounds, nonylphenols, metals, radioactive compounds, pthalates, pesticides, insecticides, herbicides, personal care products, particulate matter, etc. Several different waste matrices - agricultural, industrial, chemical manufacturing, WWTPs, etc. Media = air, land, water, wastewater. Can search by postcode.	No relevant entries

Appendix XI Information relevant to the gap analysis

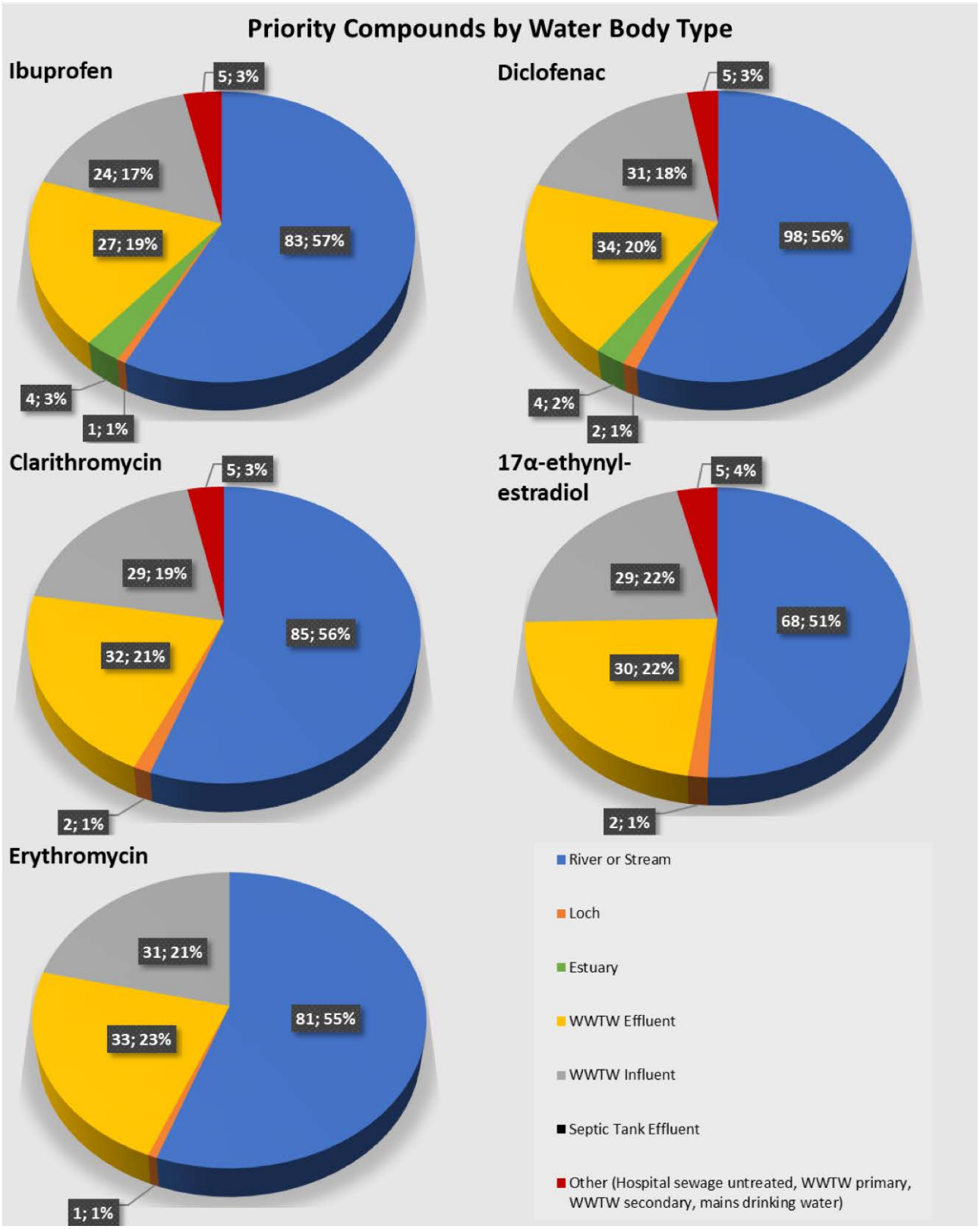


Figure a1. Water body types with monitoring data of the five priority compounds, with number of datapoints and percentage value indicated.

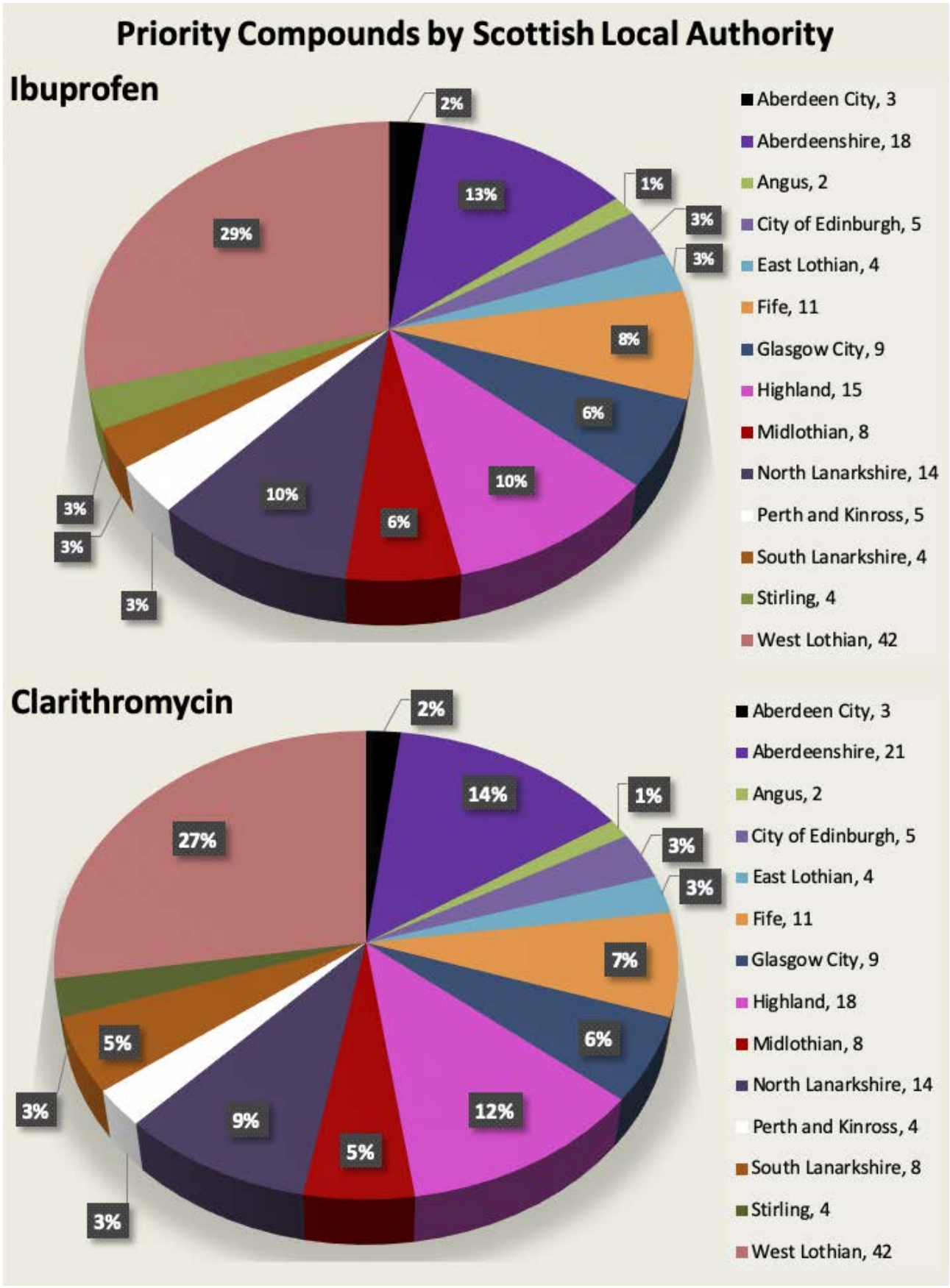
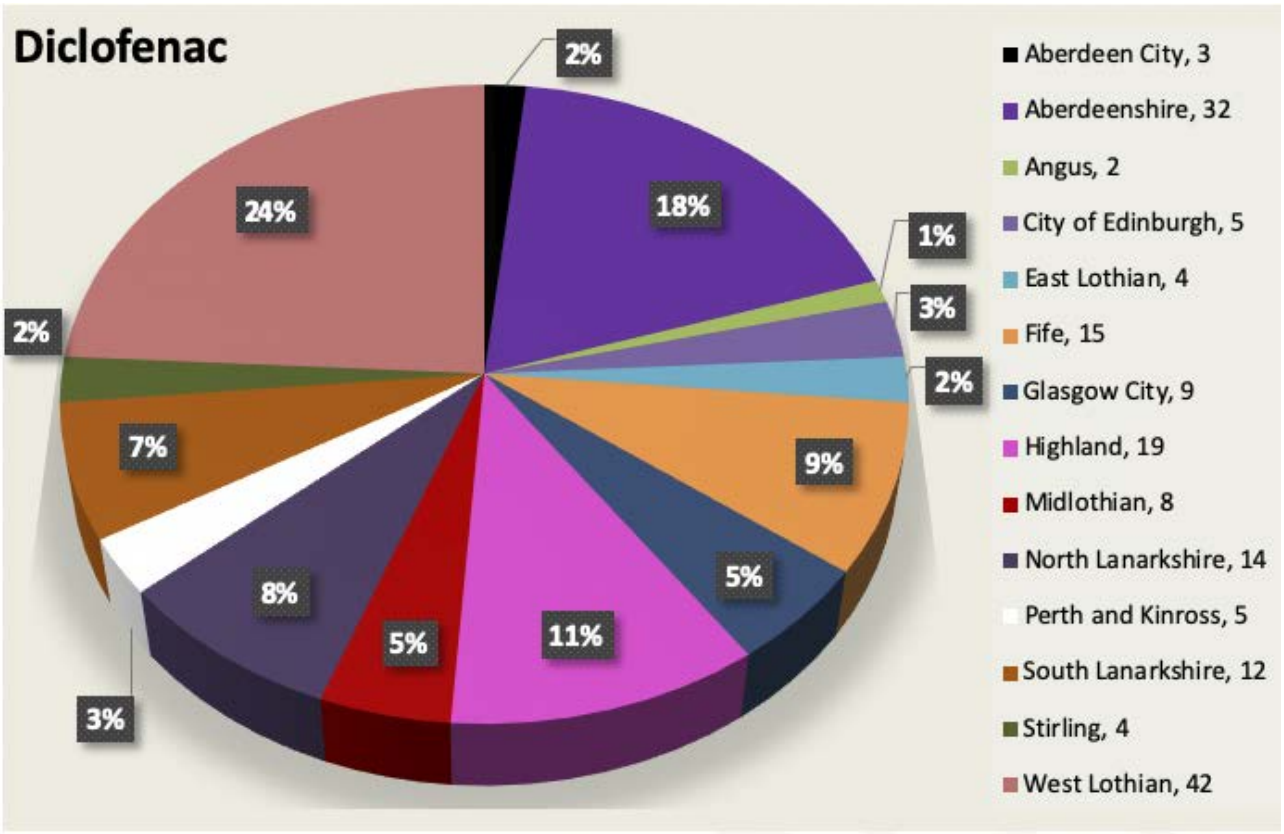


Figure a2. Scottish local authorities (14 total) with monitoring data of the five priority compounds, with number of datapoints and percentage value indicated.



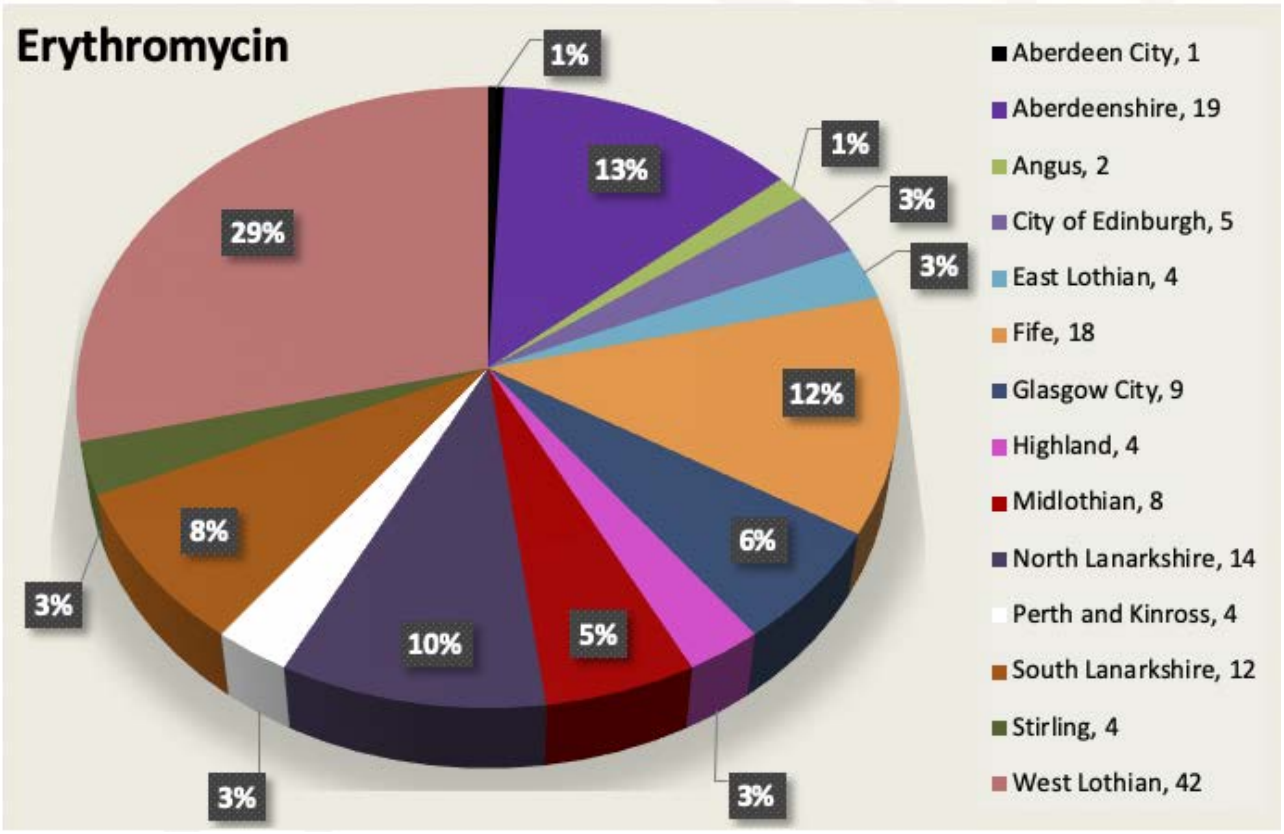


Figure a2 (cont'd). Scottish local authorities (14 total) with monitoring data of the five priority compounds, with number of datapoints and percentage value indicated.

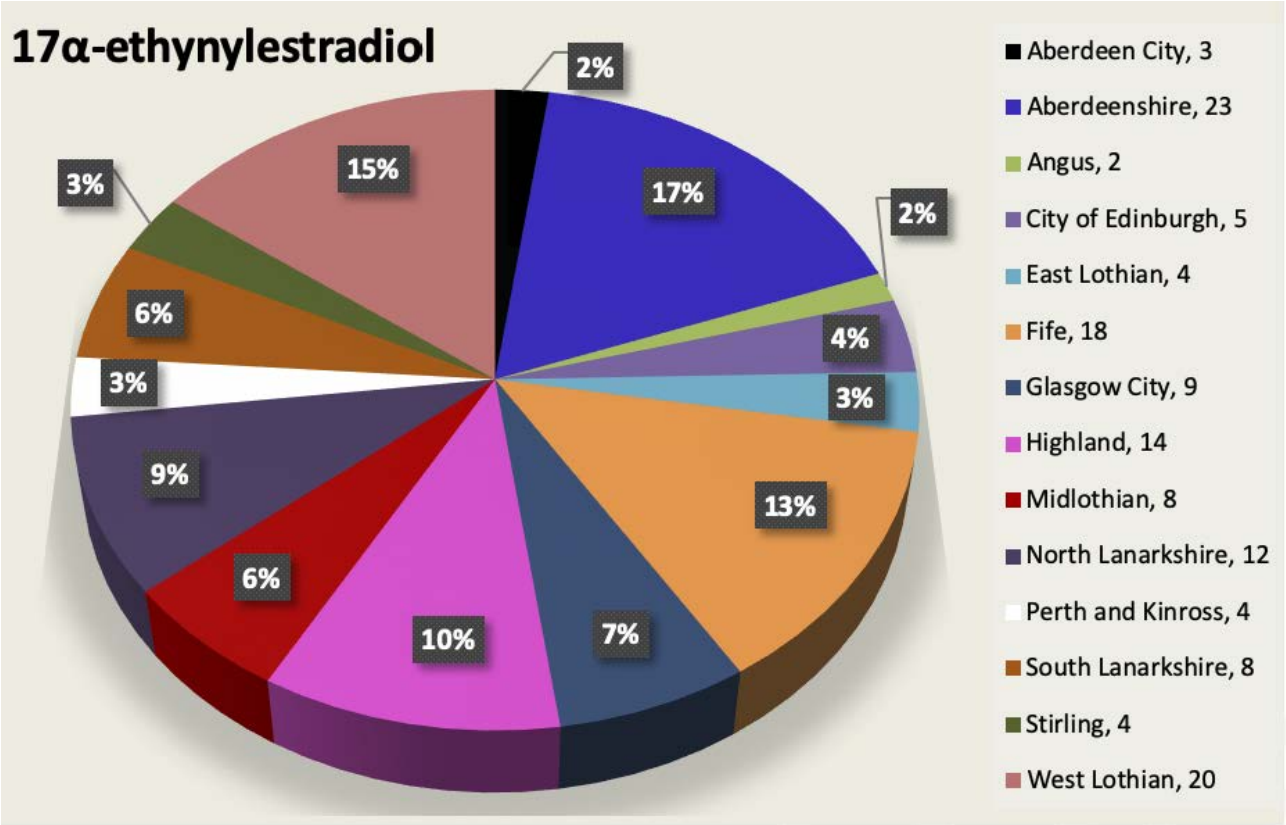


Figure a2 (cont'd). Scottish local authorities (14 total) with monitoring data of the five priority compounds, with number of datapoints and percentage value indicated.

Table a1. List of Scottish local authorities without pharmaceutical monitoring data. Population, number and types of WWTWs and hospitals in those regions included, and corresponding catchments indicated. CS = Cess & septic tanks, NWR = not WIC reportable, PRE = preliminary only, PRI = primary treatment, SEC = secondary treatment, TER = tertiary treatment. Acute = acute hospital, Mar = maternity hospital, MH = mental health hospital, MS = multi-service hospital, PRA = patient residential accommodation

Local Authority	Population[1]	WWTWs			Hospitals		
		Total, (by type)	PE range, (mean)	Catchments	Total, (by type)	Beds range, (mean)	Catchments
Argyll and Bute	85,870	150 CS = 116 NWR = 10 PRI = 2 SEC = 18 TER = 4	0 – 14,445 (547)	Appin coastal Clyde estuary Cowal/Clyde sealochs coastal Island of Mull coastal Islay coastal Kintyre coastal Knapdale coastal Loch Fyne coastal River Add River Awe River Leven (Loch Lomond) Tiree coastal	12 Other = 12	0 – 52 (13)	Cowal/Clyde sealochs coastal Island of Bute coastal Islay coastal Kintyre coastal Knapdale coastal Loch Fyne coastal
Clackmannanshire	51,540	6 CS = 1 SEC = 5	59 – 44,077 (10,138)	River Devon Stirling coastal	1 Other = 1	45	Stirling coastal
Comhairle nan Eilean Siar	26,720	170 CS = 148 PRI = 1 SEC = 21	0 – 11,605 (154)	Barra coastal Benbecula coastal Berneray coastal Eilean Arnol coastal Eriskay coastal Great Bernera coastal Lewis and Harris coastal North Uist coastal Scalpay coastal South Uist coastal	6 Acute = 1 Other = 5	0 – 85 (17)	Barra coastal Benbecula coastal Berneray coastal Lewis and Harris coastal

Local Authority	Population[1]	WWTWs			Hospitals		
		Total, (by type)	PE range, (mean)	Catchments	Total, (by type)	Beds range, (mean)	Catchments
Dumfries and Galloway	148,860	179 CS = 110 NWR = 1 PRI = 4 SEC = 48 TER = 16	0 – 43,350 (837)	Annan coastal Auchencairn Bay/ Rough estuary Bladnoch and Cree estuary Dumfries coastal Galloway coastal Gretna coastal Lochar water Piltanton and Luce estuary River Annan River Bladnoch River Cree River Dee (Solway) River Esk (Solway) River Nith Solway estuary Stewartry coastal Urr water Water of Luce	23 MH = 3 MS = 1 Other = 17 PRA = 2	0 – 85 (11)	Dumfries coastal Galloway coastal Gretna coastal River Annan River Cree River Dee (Solway) River Esk (Solway) River Nith Stewartry coastal
Dundee city	149,320	2 CS = 2	0 – 21 (10)	Dundee coastal	20 Acute = 1 MH = 1 MS = 1 Other = 17	0 – 788 (53)	Dighty water Dundee coastal
East Ayrshire	122,010	28 CS = 13 SEC = 14 TER = 1	0 – 16,628 (1,777)	River Ayr River Doon River Irvine River Nith	20 Acute = 1 Mat = 1 Other = 17 PRA = 1	0 – 560 (30)	River Ayr River Doon River Irvine River Nith
East Dunbartonshire	108,640	2 CS = 2	49 – 57 (53)	River Kelvin	5 MH = 1 Other = 3 PRA = 1	0	River Kelvin
East Renfrewshire	95,530	5 CS = 1 SEC = 2 TER = 2	26 – 54,257 (12,942)	River Garnock White Cart water	2 Other = 2	0	White Cart water

Local Authority	Population[1]	WWTWs			Hospitals		
		Total, (by type)	PE range, (mean)	Catchments	Total, (by type)	Beds range, (mean)	Catchments
Falkirk	160,890	14 CS = 1 PRI = 1 SEC = 10 TER = 2	41 – 91,701 (21,650)	Forth estuary Forth estuary (south) coastal River Avon River Carron (Falkirk) Stirling coastal	15 Acute = 1 MH = 1 Other = 11 PRA = 2	0 – 724 (62)	Forth estuary (south) coastal River Avon River Carron (Falkirk)
Inverclyde	77,800	1 SEC = 1	87,914	Inverclyde coastal	8 Acute = 2 Other = 6	0 – 343 (42)	Inverclyde coastal
Moray	95,820	63 CS = 49 PRI = 3 SEC = 10 TER = 1	0 – 44,985 (1,645)	Banff coastal Moray coastal Muckle burn River Deveron River Findhorn River Lossie River Spey	9 Acute = 1 Other = 8	0 – 178 (28)	Banff coastal Moray coastal River Deveron River Lossie River Spey
North Ayrshire	134,740	34 CS = 26 NWR = 1 PRI = 2 SEC = 3 TER = 2	4 – 332,371 (12,950)	Arran coastal Great Cumbrae coastal Inverclyde coastal River Garnock River Irvine	9 MH = 1 Other = 8	0 – 244 (29)	Arran coastal Great Cumbrae coastal North Ayrshire coastal River Garnock River Irvine
Orkney Islands	22,270	41 CS = 30 NWR = 1 SEC = 9 TER = 1	0 – 13,485 (464)	Eday coastal Flotta coastal Loch of Stenness Orkney coastal Rousay coastal Sanday coastal South Walls coastal Stronsay coastal Westray coastal	5 Acute = 1 Other = 4	0 – 49 (9)	Orkney coastal
Renfrewshire	179,100	4 CS = 1 SEC = 3	22 – 126,439 (53,028)	Black Cart water Glasgow coastal	9 Acute = 1 MH = 2 Other = 6	0 – 654 (81)	Black Cart water Glasgow coastal White Cart water

Local Authority	Population[1]	WWTWs			Hospitals		
		Total, (by type)	PE range, (mean)	Catchments	Total, (by type)	Beds range, (mean)	Catchments
Scottish Borders	115,510	97 CS = 37 PRI = 6 SEC = 42 TER = 12	0 – 30,714 (1,414)	Berwick coastal Eye water River Esk (Lothian) River Esk (Solway) River Tweed Whiteadder water	3 Acute = 1 Other = 2	0 – 267 (96)	Berwick coastal River Tweed
Shetland Islands	22,920	80 CS = 79 SEC = 1	0 – 10,517 (251)	Bressay coastal Fetlar coastal Housay coastal Shetland coastal Unst coastal West Burra coastal Whalsay coastal Yell coastal	6 Acute = 1 Other = 5	0 – 48 (8)	Fair Isle coastal Foula coastal Housay coastal Shetland coastal
South Ayrshire	112,610	22 CS = 12 SEC = 10	7 – 15,491 (1,268)	North Ayrshire coastal River Ayr River Doon River Irvine River Stinchar Water of Girvan	9 Acute = 1 MH = 2 Other = 6	0 – 334 (58)	North Ayrshire coastal River Ayr South Ayrshire coastal Water of Girvan
West Dunbartonshire	88,930	5 CS = 1 SEC = 3 TER = 1	135 – 581,220 (128,681)	Clyde estuary River Leven (Loch Lomond)	7 Acute = 1 Other = 6	0 – 168 (40)	Dumbarton coastal Glasgow coastal River Leven (Loch Lomond)

[1] Population (by the National Records for Scotland, 2019 https://www.nrscotland.gov.uk/statistics-and-data/statistics/stats-at-a-glance/council-area-profiles)

Table a2. List of Scottish local authorities with pharmaceutical monitoring data. Population, number and types of WWTWs and hospitals in those regions included, source and corresponding catchment indicated. CS = Cess & septic tanks, NWR = not WIC reportable, PRE = preliminary only, PRI = primary treatment, SEC = secondary treatment, TER = tertiary treatment. Acute = acute hospital, Mat = maternity hospital, MH = mental health hospital, MS = multi-service hospital, PRA = patient residential accommodation

Local Authorities	Population[1]	WWTWs			Hospitals		
		Total, (by type)	PE range, (mean)	Catchments	Total, (by type)	Beds range, (mean)	Catchments
Aberdeen City	228,670	6 CS = 2 SEC = 2 TER = 2	7 – 289,584 (56,254)	Buchan coastal River Dee (Grampian) River Don	22 Acute = 2 Mat = 1 MH = 2 MS = 1 Other = 14 PRA = 2	0 – 713 (63)	Aberdeen North coastal Aberdeen South coastal River Dee (Grampian) River Don
Aberdeenshire	261,210	193 CS = 111 PRE = 4 PRI = 2 SEC = 59 TER = 17	0 – 35,293 (1,089)	Banff coastal Bervie water Buchan coastal Kincardine and Angus coastal River Dee (Grampian) River Deveron River Don River North Esk (Tayside) River Ugie River Ythan Ythan estuary	19 Other = 19	0 – 39 (12)	Banff coastal Buchan coastal Kincardine and Angus coastal River Dee (Grampian) River Deveron River Don River Ugie
Angus	116,200	63 CS = 32 PRI = 1 SEC = 21 TER = 9	0 – 240,824 (5,070)	Dighty water Dundee coastal Firth of Tay Kincardine and Angus coastal Lunan water Montrose Basin River North Esk (Tayside) River South Esk (Tayside) River Tay	13 MH = 1 MS = 2 Other = 10	0 – 64 (11)	Dighty water Dundee coastal Kincardine and Angus coastal Lunan water River North Esk (Tayside) River South Esk (Tayside) River Tay
City of Edinburgh	524,930	2 TER = 2	39,818 – 764,659 (402,238)	River Almond	27 Acute = 2 MH = 1 Other = 23 PRA = 1	0 – 986 (87)	Edinburgh coastal River Almond Water of Leith

Local Authorities	Population[1]	WWTWs			Hospitals		
		Total, (by type)	PE range, (mean)	Catchments	Total, (by type)	Beds range, (mean)	Catchments
East Lothian	107,090	27 CS = 15 PRI = 2 SEC = 6 TER = 4	0 – 28,786 (2,452)	East Lothian coastal River Esk (Lothian) River Tyne	6 MH = 1 Other = 5	0 – 50 (13)	East Lothian coastal River Tyne
Fife	373,550	53 CS = 15 PRE = 6 PRI = 7 SEC = 21 TER = 4	14 – 172,355 (6,521)	Eden estuary Firth of Tay Forth estuary North Fife coastal River Eden South Fife coastal Stirling coastal	29 Acute = 2 MH = 3 Other = 24	0 – 635 (42)	North Fife coastal River Eden River Leven (Fife) South Fife coastal
Glasgow City	633,120	3 SEC = 2 TER = 1	232,840 – 563,713 (371,493)	Clyde estuary River Clyde	48 Acute = 6 MH = 5 Other = 37	0 – 1607 (78)	Glasgow coastal River Clyde River Kelvin White Cart water

Local Authorities	Population[1]	WWTWs			Hospitals		
		Total, (by type)	PE range, (mean)	Catchments	Total, (by type)	Beds range, (mean)	Catchments
Highland	235,830	302 CS = 208 PRE = 1 PRI = 3 SEC = 73 TER = 17	0 – 85,623 (856)	Appin coastal Ardgour coastal Ardnamurchan coastal Beauly/Inverness firth Beauly coastal Brora coastal Cromarty coastal Cromarty firth Dornoch coastal Dornoch firth Forss water Inverness coastal Isle of Skye coastal Loch Linnhe Minch coastal Muckle burn River Alness River Beauly River Cassley River Nonon River Ewe River Findhorn River Fleet River Glass River Helmsdale River Leven (Lochaber) River Lochy River Morar River Nairn River Naver River Ness River Oykel River Shiel River Shin River Spey River Thurso Sounds coastal Thurso coastal Tongue coastal Wick coastal Wick river	60 Acute = 1 MH = 1 MS = 1 Other = 57	0 – 447 (14)	Appin coastal Ardnamurchan coastal Brora coastal Cromarty coastal Dornoch coastal Inverness coastal Isle of Skye coastal Minch coastal Moray coastal River Nairn River Ness River Spey River Thurso Sounds coastal Thurso coastal Tongue coastal Torridon coastal Wick coastal
Midlothian	92,460	14 CS = 5 SEC = 7 TER = 2	2 – 13,190 (1,595)	River Esk (Lothian) River Tyne	3 Other = 2 PRA = 1	0	River Esk (Lothian)

Local Authorities	Population[1]	WWTWs			Hospitals		
		Total, (by type)	PE range, (mean)	Catchments	Total, (by type)	Beds range, (mean)	Catchments
North Lanarkshire	341,370	15 CS = 3 SEC = 6 TER = 6	23 – 48,319 (8,098)	River Almond River Avon River Carron (Falkirk) River Clyde River Kelvin	10 Acute = 2 MS = 1 Other = 7	0 – 622 (121)	River Clyde River Kelvin
South Lanarkshire	320,530	124 CS = 97 SEC = 18 TER = 9	0 – 63,430 (1,876)	River Clyde River Tweed White Cart water	15 Acute = 1 MH = 2 MS = 1 Other = 11	0 – 490 (51)	River Clyde River Tweed White Cart water
Perth and Kinross	151,950	89 CS = 42 SEC = 34 TER = 11	3 – 100,352 (2,128)	Allan water Dundee coastal Earn coastal Firth of Tay Perth coastal River Devon River Earn River Leven (Fife) River Tay Stirling Coastal	14 MH = 1 MS = 1 Other = 12	0 – 209 (31)	Earn coastal Perth coastal River Earn River Leven (Fife) River Tay
Stirling	94,210	38 CS = 8 PRI = 1 SEC = 25 TER = 4	17 – 78,107 (3,079)	Allan water Forth estuary Forth estuary (South) coastal River Earn River Forth River Leven (Loch Lomond) River Tay Stirling coastal	8 Other = 6 PRA = 2	0	Allan water Forth estuary (South) coastal River Tay Stirling coastal
West Lothian	183,100	22 CS = 5 PRI = 1 SEC = 7 TER = 9	8 – 115,185 (9,786)	Forth estuary (South) coastal River Almond River Avon	10 Acute = 1 Other = 7 PRA = 2	0 – 427 (52)	River Almond River Avon

[1] Population (by the National Records for Scotland, 2019 https://www.nrscotland.gov.uk/statistics-and-data/statistics/stats-at-a-glance/council-area-profiles)

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