Pharmaceuticals in the Environment

As a responsible healthcare company, we are committed to the health and safety of our society and planet. We make it a priority to effectively manage the risks associated with pharmaceuticals in the environment (PIE).

MedImmune AstraZeneca

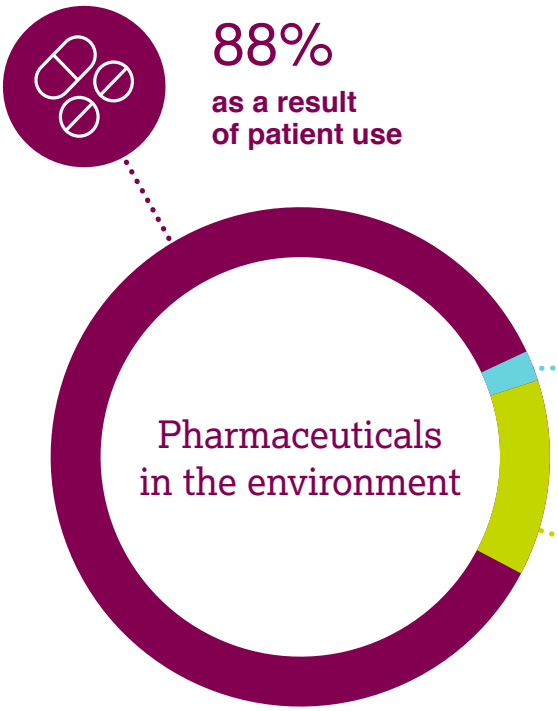
How do Pharmaceutical Products get into the Environment?

Pharmaceuticals enter the environmental mainly as a result of patient use, where they can pass through our bodies and into waterways. Drug manufacture and the improper disposal of unused medicines also add to the trace levels of pharmaceuticals in rivers, lakes, soils, and, sometimes, drinking water. AstraZeneca recognises that, even in such low concentrations, the risks associated with Pharmaceuticals in the Environment (PIE) should be determined, minimised and managed.

AstraZeneca supports actions based on scientific evidence to address the challenges presented by PIE. These include:

- Assessing the environmental risk of our medicines to support drug marketing authorisations
- Actively managing the environmental risks resulting from our manufacturing
- Supporting industry and government efforts to improve medicine disposal programs and education
- Co-sponsoring research to fill scientific gaps to understand and mitigate the risks of PIE.

To learn more about the risks associated with PIE and what we are doing to manage them please click **here.**



Societal Concerns about PIE

Trace amounts of pharmaceuticals have been detected in the environment for more than 20 years. As environmental monitoring expands and the methods for measuring pharmaceuticals in the environment become more sophisticated and detection limits get better, the geographical scope and number of pharmaceuticals measured in the environment will grow. We also recognise that these concerns will increase with improved access to medicines and an ageing population where more patients will pass pharmaceutical residues into the environment.

In most cases, environmental monitoring demonstrates that PIE resulting from patient use poses low or insignificant environment risk and the presence of these trace levels does not cause a problem. However, there can be some location-specific environmental risks for some particular pharmaceuticals, especially in regions where there may be inadequate sewage treatment, high populations of people and rivers with low flow conditions. We need to be sure we have tools to identify these 'at risk' situations and to devise appropriate solutions.

The issue of PIE is gaining attention outside the scientific community, with increased scrutiny from media, governments, regulatory agencies, and investors. The concerns about PIE have been recognised by the United Nations Environment Programme and the World Health Organization (WHO) within its Strategic Approach to International Chemicals Management, where Environmentally Persistent Pharmaceutical Pollutants (EPPP) has been included as an emerging policy issue. **For more information on EPPP click here**.

Risks to Human Health and the Environment

There are currently no reports of adverse human health effects attributed to pharmaceuticals in environmental waters. Studies from the World Health Organization concluded, **"Trace quantities of pharmaceuticals in drinking water are very unlikely to pose risks to human health because of the substantial margin of exposure or margin of safety between the concentrations detected and the concentrations likely to evoke a pharmacological effect."** Further, **"Concerns over pharmaceuticals should not divert the attention and valuable resources of water suppliers and regulators from the various bacterial, viral and protozoan waterborne pathogens and other chemical priorities, such as lead and arsenic."**

While trace concentrations of pharmaceuticals in drinking water are very unlikely to pose risks to human health, knowledge gaps still exist.

However, the risks associated with long-term exposure to low concentrations of pharmaceuticals and the combined effects of mixtures of pharmaceuticals and other compounds still requires further investigation[1].

It is generally considered that levels of pharmaceuticals in the environment are below those which would result in acute (short-term) effects in wildlife, including aquatic life such as fish. Ongoing, concerns that chronic (long-term) exposure to these trace levels could result in a potential risk to organisms do exist. Most of these concerns focused on the potential developmental and reproductive effects of medicines that are designed to interact with the human endocrine or hormone system (for example, contraceptives, hormone replacement therapies and certain cancer treatments). It has been shown that some endocrine active chemicals can have chronic impacts on the sexual development of fish. However, these effects are not just limited to pharmaceuticals. They have been shown to also be caused by exposure to natural hormones and other manmade chemicals present in the environment.

Further studies are needed to determine if there are any significant population-level environmental effects arising from long-term and low-level exposure to pharmaceuticals in environmental waters. There is one well known case where a non-AstraZeneca medicine has caused a population level impact on wildlife. The veterinary use of diclofenac in Asia resulted in the death of millions of vultures that fed on treated cattle. This impact was unexpected as the exposure resulted from cultural farming practices not captured in environmental risk assessment guidance and shows the importance for ongoing vigilance.

There is also growing concern over the antimicrobial resistance and the role that antibiotic residues in the environment has in causing resistance to antibiotic treatment.

[1]WHO. (2011). Pharmaceuticals in Drinking Water. WHO Press, Geneva, Switzerland. Link to report

AstraZeneca's Position

AstraZeneca is committed to ensuring the effective environmental management of our products across the whole of the product life cycle – from drug development and manufacture through to patient use and disposal.

To do this we:

- **Conduct an Environmental Risk Assessment (ERA) before the approval of a new medicine. We do this by generating environmental fate and toxicity data according to international standards. In an ERA we identify safe concentrations of a pharmaceutical. We submit the resulting data to Regulatory Authorities as formal ERA reports. The environmental risk associated with biological therapies is considered negligible and they currently require a case-by-case exemption for an ERA.**
- **Make our ERA data available via our webpages and in Appendix 1 of this document.**
- **Establish safe discharge concentrations for our manufacturing operations and report our compliance against these safe discharge standards.**
- **Conduct ecopharmacovigilance (EPV) to ensure that our ERAs and safe discharge concentrations remain up to date and reflect the latest science[2]. Our EPV process reviews emerging science and literature, looking for new information that might change the way we assess the environmental risks associated with our APIs. Our EPV is critical in helping us to ensure the environmental safety of our products.**
- **Actively encourage our patients to return unwanted medicines for safe disposal through collection schemes. We support initiatives aimed at improving patient awareness of medicines and sharps takeback, in addition to contributing to the funding of a number of collection schemes.**
- **Conduct targeted environmental research to address our critical knowledge gaps and improve the level of environmental protection we offer.**

[2]Holm et al (2013) Ecopharmacovigilance in Practice: Challenges and Potential Opportunities. Drug Safety Volume 36, Issue 7, pp 533–546.

Safe Discharges of Active Pharmaceutical Ingredients

While waste from the manufacture of medicines is only a small proportion of the pharmaceuticals found in the environment, it is an area that AstraZeneca can make a direct impact.

While there are currently no regulatory requirements, we set safe discharge concentrations for our own production sites and those of our suppliers.

We have two safe discharge concentrations for each pharmaceutical; one for long-term exposure called an Environmental Reference Concentration (ERC) and one for short-term exposure called a Maximum Tolerable Concentration (MTCs). Our safe discharge approach[4] is based on established environmental quality standards and considers indirect exposure of fish-eating mammals and humans, as well as pharmaceutical impacts on aquatic wildlife (e.g. algae, invertebrates and fish). These values must not be exceeded in the environmental waters downstream of our pharmaceutical production sites.

We actively share our Environmental Reference Concentration and Maximum Tolerable Concentration methodology with key suppliers and require them to risk assess and manage emissions associated with the APIs they manufacture or formulate on our behalf. These values are described in Appendix 2.

We have an annual review programme to confirm compliance with these safe discharge concentrations.

From 2009–2011 we conducted a comprehensive site effluent project, which measured API effluent concentrations across all our own manufacturing sites globally. The project demonstrated a good correlation between predicted discharge concentration and measured concentrations. To date, the majority of assessments have demonstrated safe discharges without the need for any intervention in our normal effluent-handling processes. In cases where a potential environmental risk has been identified, we have collaborated with the site to understand and manage the relevant discharge. Where a theoretical assessment has been performed, chemical analysis of the effluent at the site boundary may be recommended to reduce any uncertainty within the exposure assessment. If the potential risk remains, intervention to reduce the pharmaceutical concentration in the effluent is required.

Ensuring that our manufacturing discharges are safe is a key design principle when bringing new production and formulation processes on line.

We have described our approach to safe discharges in a recent article in the *Chemical Engineer*[5].

AstraZeneca also participates in the Pharmaceutical Supply Chain Initiative (PSCI) and the European Federation of Pharmaceutical Industry Association (Efpia) approaches to ensure responsible effluent management.

[4]Murray-smith et al (2012) Managing emissions of active pharmaceutical ingredients from manufacturing facilities: An environmental quality standard approach. Integrated Environmental Assessment and Management, 8: 320–330

[5]Hargreaves et al (2017). Something in the Water: Managing the safe discharge of active pharmaceutical ingredients during drug production. The Chemical Engineer, November 36-41.

Providing Scientific Leadership

We aim to lead our industry in understanding and mitigating the environmental risks of pharmaceuticals.

AstraZeneca sits on the governance team of the European Federation of Pharmaceutical Industry Associations (Efpia), Medicines for Europe and the Association of European Self-Medication Industry (AESGP) PIE task force that advocates an eco-pharmaco-stewardship (EPS) approach. **For more information on EPS click here.** EPS considers the entire life-cycle of a medicine and addresses the roles and responsibilities of all stakeholders involved in delivering a sustainable approach to pharmaceutical use. These stakeholders include government, regulatory agencies, public and private healthcare providers, the pharmaceutical industry, environmental experts, doctors, pharmacists, water treatment companies, and patients.

EPS has three priorities to help manage the environmental risks associated with human pharmaceuticals:

1. **The identification of the environmental risks of (i) established pharmaceuticals that lack environmental data and (ii) novel pharmaceuticals earlier within pharmaceutical development through intelligent and targeted assessment strategies (IMI iPiE Project)**
2. **Environmentally responsible pharmaceutical manufacturing including the development of best practice approaches to enable manufacturers to minimise losses to the environment[6], and,**
3. **An extended environmental risk assessment (eERA) framework to manage environmental risks throughout the lifecycle of a medicine and to ensure that ERAs remain up-to-date and relevant.**

AstraZeneca actively participates in developing and executing these industry-wide initiatives. For example, company representatives sit on the executive team for the Innovative Medicines Initiative iPiE project and lead its research on the prioritisation of established medicines for environmental testing.

[6]Caldwell, D. J. et al. (2016), A risk-based approach to managing active pharmaceutical ingredients in manufacturing effluent. Environmental Toxicology and Chemistry, 35: 813-822.

PIE Research

We carefully monitor and actively contribute the scientific research published on PIE, in particular, studies that describe the effects that pharmaceutical products may have on wildlife and human health.

As a science-based company we support the use of science-led environmental risk assessments. We actively collaborate with regulatory, academic, health care and research organisations to identify additional data needs on the environmental transport, fate and effects of pharmaceuticals. We are a partner with the Innovative Medicines Initiative project on PIE (iPIE) and have committed to providing data for analysis and new studies to fill critical data gaps. Select peer-reviewed publications resulting from AstraZeneca funded research are highlighted in Appendix 3.

We have a dedicated PIE research programme and we are currently co-sponsoring research to:

- **Predict and identify environmental hazards and risks earlier in pharmaceutical development**
- **Develop and validate approaches to prioritise established APIs that lack environmental data for further investigation**
- **Assess the environmental impact of our innovative medicines where existing regulatory approaches may not be fit for purpose**
- **Assess the risks of pharmaceuticals in low-and middle-income countries that have different levels of waste water treatment and different water use and re-use patterns**
- **Improve the environmental and human health assessment of antibiotics and AMR**

IFPMA AMR Alliance and Roadmap on AMR

The emergence of infectious diseases resistant to many antibiotics is an urgent global issue that may compromise basic surgical operations and treatment in the future. While AstraZeneca has prioritised research and development into non-communicable disease, we stand with our colleagues across the industry, health leaders, patients, physicians and governments around the world to develop a multi-stakeholder approach to tackle the global threat that antimicrobial resistance (AMR) poses to society and the barriers that prevent new antibiotics coming to the market.

In January 2016, we signed the Davos Declaration on Combating Antimicrobial Resistance along with over 100 other companies (**AMR Declaration**). The Declaration is a collective call on governments to commit to the investment needed to support the development of new antibiotic therapies. In September 2016, together with 12 other companies, we signed the AMR Roadmap presented to the United Nations General Assembly (**AMR Roadmap**). The AMR Industry Alliance brings together the signatories of the Davos declaration and AMR Roadmap to drive and measure the life-sciences' industry progress to curb antimicrobial resistance.

To tackle the environmental aspects of the threat posed by AMR and our public commitments to the AMR roadmap, we are co-funding research that aims to develop and validate new regulatory protection goals for AMR development in the environment. These projects will establish approaches to define safe environmental levels for antibiotics entering the environment through drug production and patient use[7].

[7]Le Page, G. et al. (2017). Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity and antimicrobial resistance. Environment International, 109, 155-169. doi:https://doi.org/10.1016/j.envint.2017.09.013

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Appendix 1

Environmental risk data relating to our medicines

As part of AstraZeneca's commitment to making our science accessible, we provide environmental risk summaries for the pharmaceuticals used in our global brands.

The summaries are consistent with the environmental information provided as part of our marketing applications, or where this is not available, from currently available data including reliable scientific literature.

For each pharmaceutical, the potential environmental risk is calculated to determine if any adverse effects on the environment might be expected to occur. To make our environmental risk assessments more environmentally relevant we determine the environmental exposure based on the total consumption of that medicine. This approach provides a much more realistic and protective assessment of environmental risk than our regulatory submissions.

We divide environmental risk into four different categories depending on the ratio between the predicted environmental concentration (PEC), that determines how much of the pharmaceutical we expect to be found in the environment river, and the predicted no effect concentration (PNEC), the level that is safe to wildlife. The four categories we use, described in the next column, are consistent with the classification system[3] for environmental information on www.fass.se, the web version of the Swedish Prescribing guide.

[3]Environmental classification of pharmaceuticals at www.fass.se: Guidance for pharmaceutical companies. 2012. https://www.fass.se/pdf/Environmental_classification_of_pharmaceuticals-120816.pdf

Generic name	AstraZeneca Brand name	Therapy area	Environmental Risk
Aclidium bromide	Eklira Duaklir (formoterol fumerate)	Respiratory	*
Anastrozole	Arimidex	Oncology	Insignificant
Atenolol	Tenormin/Tenormine/ Prenormine/ Atenol Nif-Ten (nifedipine) Tenoretic, (chlorthalidone)	Cardiovascular & Metabolic Disease	Insignificant
Bambuterol hydrochloride	Bambec and Oxeol	Respiratory	Insignificant
Bicalutamide	Casodex	Oncology	Insignificant
Budesonide	Pulmicort Rhiocort Symbicort (formoterol fumerate)	Respiratory	Insignificant
Bupivacaine hydrochloride	Marcaine and Sensorcaine	Neuroscience	*
Candesartan cilexetil	Atacand Atacand Duo (Felodipine) Atacand Plus (hydrochlorothiazide)	Cardiovascular & Metabolic Disease	Insignificant
Ceftaroline fosamil	Zinforo	Infection and Vaccines	Insignificant
Chlorthalidone	Tenoretic (atenolol)	Cardiovascular & Metabolic Disease	Insignificant
Dapagliflozin	Forxiga Xigduo (metformin) Qtern (saxagliptin)	Cardiovascular & Metabolic Disease	Insignificant
Esomeprazole sodium/magnesium	Nexium Vimovo (naproxen)	Gastrointestinal	Insignificant
Exenatide	Bydureon	Cardiovascular & Metabolic Disease	Insignificant**
Felodipine	Plendil/Modip/Splendil/ Munobal/ Flodil Atacand Duo (candesartan)	Cardiovascular & Metabolic Disease	Low
Formoterol fumarate	Oxis Symbicort (budesonide) Duaklir (Aclidium bromide)	Respiratory	Insignificant
Fulvestrant	Faslodex	Oncology	Low
Gefitinib	Iressa	Oncology	Insignificant
Goserelin acetate	Zoladex	Oncology	Insignificant**
Hydrochlorothiazide	Zestoretic (lisinopril dehydrate) Atacand Plus (candesartan cilexetil)	Cardiovascular & Metabolic Disease	Insignificant
Influenza vaccine, live, attenuated	Fluenz Tetra/ Flumist Quadrivalent	Infection and Vaccines	Low**
Isosorbide-5-mononitrate	Imdur/Duronitrin	Cardiovascular & Metabolic Disease	*
Lidocaine hydrochloride	Xylocaine EMLA (prilocaine)	Neuroscience	Insignificant
Lisinopril dihydrate	Zestril Zestoretic (hydrochlorothiazide)	Cardiovascular & Metabolic Disease	Insignificant
Mepivacaine hydrochloride	Carbocaine	Neuroscience	*
Meropenem	Merrem/Meronem	Infection and Vaccines	Insignificant
Metformin hydrochloride	Kombiglyze (saxagliptin) Xigduo (dapagliflozin)	Cardiovascular & Metabolic Disease	Low

Appendix 1

The risk categories are as follows:

- **PEC/PNEC ≤ 0.1 Use of the substance has been considered to result in insignificant environmental risk.**
- **0.1 < PEC/PNEC ≤ 1 Use of the substance has been considered to result in low environmental risk.**
- **1 < PEC/PNEC ≤ 10 Use of the substance has been considered to result in moderate environmental risk.**
- **PEC/PNEC > 10 Use of the substance has been considered to result in high environmental risk.**

The table opposite provides an overview of the environmental risk of AstraZeneca's medicines. This information will be updated as new data become available. The active pharmaceutical ingredients are listed alphabetically by their generic name. Where an API is used in a combination product (a medicine that contains more than one API) the brand name is followed by the generic name of the additional API contained within the product, in parenthesis.

For human pharmaceuticals, it is primarily the aquatic compartment that is of interest, since human medicines may be excreted partly or wholly unchanged by patients, subsequently entering the sewage system and ultimately rivers and other surface waters. The PEC is calculated using a worst-case scenario, assuming no metabolism by the patient or removal/degradation of the API during sewage treatment and using the total sales volumes for the API in the European country with the highest per capita use[1]. The sales volumes are based on all human medicines containing the API, including products marketed by other companies, where applicable. The PNEC is estimated by division of the lowest value for toxicity with the relevant assessment factor, as outlined by the European Chemicals Agency[2] and European Medicines Agency[3].

Generic name	AstraZeneca Brand name	Therapy area	Environmental Risk
Metoprolol succinate/tartrate	Seloken/Seloken ZOK/ Toprol-XL/ Betaloc/Betaloc ZOK Logimax (felodipine)	Cardiovascular & Metabolic Disease	Low
Naloxegol	Movantik/Moventig	Neuroscience	Insignificant
Naproxen	Vimovo (espmeprazole)	Gastrointestinal	Low
Nifedipine	Nif-Ten (atenolol)	Cardiovascular & Metabolic Disease	*
Olaparib	Lynparza	Oncology	Insignificant
Omeprazole	Losec/Gastroloc/Mopral/ Omepral/ Prilosec	Gastrointestinal	Insignificant***
Osimertinib mesylate	Tagrisso	Oncology	Insignificant
Palivizumab	Synagis	Infection and Vaccines	Insignificant**
Pramlintide	Symlin	Cardiovascular & Metabolic Disease	Insignificant**
Prilocaine hydrochloride	Citanest Citanest Adrenaline (adrenaline) EMLA (lidocaine)	Neuroscience	Insignificant
Propofol	Diprivan	Neuroscience	Low
Propranolol hydrochloride	Inderal	Cardiovascular & Metabolic Disease	Low
Quetiapine fumarate	Seroquel	Neuroscience	Low
Ramipril	Ramace/Hypren/ Pramace/Unipril/ Vesdil. Unimax (felodipine)	Cardiovascular & Metabolic Disease	Insignificant
Roflumilast	Daxas	Respiratory	Insignificant
Ropivacaine hydrochloride monohydrate	Naropin	Neuroscience	Insignificant
Rosuvastatin calcium	Crestor	Cardiovascular & Metabolic Disease	Low
Saxagliptin	Onglyza Kombiglyze (metformin) Qtern (dapagliflozin)	Cardiovascular & Metabolic Disease	Insignificant
Tamoxifen citrate	Nolvadex	Oncology	Low
Terbutaline sulphate	Bricanyl Respules	Respiratory	Insignificant
Ticagrelor	Brilinta/Brilique	Cardiovascular & Metabolic Disease	Insignificant
Vandetanib	Caprelsa	Oncology	Insignificant
Zafirlukast	Accolate/Accoleit/ Vanticon	Respiratory	Insignificant
Zolmitriptan	Zomig/Zomig Rapimelt/ Zomig Nasal Spray/Zomigon	Neuroscience	Insignificant

1: Per capita use calculated from kg sales data provided by IMS Health, MIDAS International Data 2016 (Visit IMS Health) for 22 European markets (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Romania, Slovakia, Spain, Sweden, Switzerland and United Kingdom), and population data taken from Eurostat (Visit Eurostat).

2: Guidance on information requirements and chemical safety assessment, 2008, Chapter R.10: Characterisation of dose [concentration]-response for environment (View guidance)

3: Guideline on the Environmental Risk Assessment of Medicinal Products for HumanUse, 2006, EMEA/CPMP/SWP/4447/00 corr2 (View guide).

* Insufficient data available

** A PEC/PNEC ratio has not been calculated. The active pharmaceutical ingredient consists of amino acids/peptides/proteins/carbohydrates/lipids, due to their nature, these products are expected to undergo very rapid and extensive degradation and are unlikely to result in a significant risk to the environment.

*** Omeprazole is the R-enantiomer of the racemate Esomeprazole (S-enantiomer). In the absence of comprehensive environmental data for omeprazole, the more scientifically robust long-term data set for esomeprazole has been used to calculate the PNEC and total sales of both esomeprazole and omeprazole are included in the calculation of the PEC.

Appendix 2

Safe discharge concentrations relating to our medicines

The table opposite provides an overview of the safe discharge concentrations for AstraZeneca's medicines. Safe concentrations are provided for discharges entering freshwater and marine environments, depending on where the API manufacturing or formulation site discharges. Our safe discharge approach is based on established environmental quality standards and considers indirect exposure of fish-eating mammals and humans, as well as pharmaceutical impacts on aquatic wildlife (e.g. algae, invertebrates and fish). These values must not be exceeded in the waters downstream of our pharmaceutical production sites. The lowest of the two safe discharge concentrations for each pharmaceutical; one for long-term exposure called an Environmental Reference Concentrations (ERC) and one for short-term exposure called a Maximum Tolerable Concentrations (MTCs) are provided for freshwater and marine sites.

Active Pharmaceutical Ingredient	Lowest ERC for discharges to freshwater (µg/L)	Lowest MTC for discharges to freshwater (µg/L)	Lowest ERC for discharges to salt water [marine] (µg/L)	Lowest MTC for discharges to salt water [marine] (µg/L)
active pharmaceutical ingredient with generic value	0.1	0.1	0.1	0.1
allopurinol	14	14	1.4	14
anastrozole	0.17	0.17	0.1	0.17
atenolol	150	210	15	33
avibactam	200	1200	20	120
bambuterol	71	140	7.1	71
bicalutamide	1	2.5	0.1	1
budesonide	0.024	0.024	0.024	0.024
bupivacaine	12	12	3.9	12
candesartan	4.2	4.2	4.2	4.2
candesartan cilexetil	0.012	3.9	0.0012	3.9
cediranib	0.032	0.8	0.0032	0.3
ceftaroline	0.61	0.61	0.061	0.061
ceftazidime	1.3	1.3	0.13	0.13
chlorthalidone	70	100	8	80
clomethiazole	62	620	6.2	62
dapagliflozin	4.2	4.2	4.2	4.2
esomeprazole	83	210	8.3	42
felodipine	0.005	0.5	0.0005	0.05
formoterol	0.006	0.16	0.006	0.16
fulvestrant	0.00057	0.0057	0.000057	0.00057
gefitinib	0.52	8.3	0.052	2.2
hydrochlorothiazide	6.3	53	0.63	34
isosorbide-5-mononitrate	120	127	12	120
lesinurad	200	211	20	120
lidocaine	67	67	11	67
lisinopril	8.4	8.4	8.4	8.4
mepivacaine	59	140	5.9	59
meropenum	1.1	1.5	0.15	0.15
metformin	100	1300	10	130
metoprolol	7.3	73	0.73	7.3
naloxegol	200	210	20	120
naproxen	4.2	270	0.42	27
olaparib	0.24	0.24	0.024	0.024
omeprazole	83	419	8.3	41.9
osimertinib	0.075	0.75	0.0075	0.075
prilocaine	3.2	3.2	3.2	3.2
propofol	0.37	3.7	0.037	0.37
propranolol	0.23	4.6	0.023	0.46
quetiapine	8	84	0.8	15
ramipril	0.052	0.052	0.052	0.052
roflumilast	0.084	0.28	0.0084	0.084
ropivacaine	26	340	3.4	34
rosuvastatin	1.8	14	0.18	14
saxagliptin	4	14	0.4	14
selumetinib	4.4	4.4	4.2	4.2
tamoxifen	0.2	0.49	0.049	0.049
terbutaline	3.5	3.5	3.5	3.5
ticagrelor	37	37	5.3	5.3
vandetanib	0.67	3	0.067	0.3
zafirlukast	13	37	1.3	3.7
zolmitriptan	2.1	2.1	2.1	2.1

Appendix 3

Selected peer reviewed publications to advance the science on the environmental risks of pharmaceuticals

Improve the environmental and human health assessment of antibiotics and AMR

Ashbolt NJ, Amézquita A, Backhaus T, Borriello P, Brandt KK, Collignon P, . . . Topp E. 2013. **Human Health Risk Assessment (HHRA) for Environmental Development and Transfer of Antibiotic Resistance**. Environmental Health Perspectives 121(9): 993-1001

Brandt KK, Amézquita A, Backhaus T, Boxall A, Coors A, Heberer T, . . . Topp E. 2015. **Ecotoxicological assessment of antibiotics: A call for improved consideration of microorganisms.** Environment International 85: 189-205

Jong M-C, Su J-Q, Bunce JT, Harwood CR, Snape JR, Zhu Y-G, Graham DW. 2018. **Co-optimization of sponge-core bioreactors for removing total nitrogen and antibiotic resistance genes from domestic wastewater.** Science of The Total Environment 634: 1417-1423

Larsson DGJ, Andremont A, Bengtsson-Palme J, Brandt KK, de Roda Husman AM, Fagerstedt P, . . . Wernersson A-S. 2018. **Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance.** Environment International 117: 132-138

Le Page G, Gunnarsson L, Snape J, Tyler CR. 2017. **Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity and antimicrobial resistance**. Environment International 109: 155-169

Pruden A, Larsson DGJ, Amézquita A, Collignon P, Brandt KK, Graham DW, . . . Zhu Y-G. 2013. **Management Options for Reducing the Release of Antibiotics and Antibiotic Resistance Genes to the Environment.** Environmental Health Perspectives 121(8): 878-885

Assess the risks of pharmaceuticals in low-and middle-income countries that have different levels of waste water treatment and different water use and re-use patterns

Bagnis S, Fitzsimons M, Snape JR, Tappin A, Comber S. 2018. **Sorption of active pharmaceutical ingredients in untreated wastewater effluent and effect of dilution in freshwater: Implications for an "impact zone" environmental risk assessment approach.** Science of The Total Environment 624: 333-341

Bagnis S, Fitzsimons MF, Snape J, Tappin A, Comber S. 2018. **Processes of distribution of pharmaceuticals in surface freshwaters: implications for risk assessment.** Environmental Chemistry Letters

Lees K, Fitzsimons M, Snape J, Tappin A, Comber S. 2016. **Pharmaceuticals in soils of lower income countries: Physico-chemical fate and risks from wastewater irrigation.** Environment International 94: 712-723

Lees K, Fitzsimons M, Snape J, Tappin A, Comber S. 2018. **Soil sterilisation methods for use in OECD 106: How effective are they?** Chemosphere 209: 61-67

Assess the environmental impact of our innovative medicines where existing regulatory approaches may not be fit for purpose

Ankley GT, Daston GP, Degitz SJ, Denslow ND, Hoke RA, Kennedy SW, . . . Versteeg D. 2006. **Toxicogenomics in Regulatory Ecotoxicology.** Environmental Science & Technology 40(13): 4055-4065

Arnold KE, Boxall ABA, Brown AR, Cuthbert RJ, Gaw S, Hutchinson TH, Jobling S, Madden JC, Metcalfe CD, Naidoo V, Shore RF, Smits JE, Taggart MA, Thompson HM. 2013. **Assessing the exposure risk and impacts of pharmaceuticals in the environment on individuals and ecosystems.** Biology Letters 9: 0492

Anette K, Alder AC, Escher BI, Duis K, Fenner K, Garric J, Hutchinson TH, Lapen DR, Péry A, Römbke J, Snape J, Ternes T, Topp E, Wehrhan A, Knacker T. 2010. **Environmental risk assessment of human pharmaceuticals in the European Union: A case study with the β-blocker atenolol.** Integrated Environmental Assessment and Management 6(S1): 514-523

Länge R, Hutchinson TH, Croudace CP, Siegmund F, Schweinfurth H, Hampe P, Panter GH, Sumpter JP. 2001. **Effects of the synthetic oestrogen17 a -ethinylestradiol over the life-cycle of the fathead minnow.** Environmental Toxicology and Chemistry 20: 1216 – 1227

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