The fate of APIs

Pharmaceuticals, their metabolites and products of incomplete degradation are present in the environment and their fate and effects are not yet fully understood.[1] Building upon the previous lesson on Pharmaceuticals in the Environment, this module looks more in depth at the fate of APIs including routes into the environment, adsorption and decomposition pathways including case studies on the breakdown products of several specific APIs.

Learning Objectives

By the end of this module you should:

- Be aware of concerns surrounding pharmaceuticals in the environment;
- Understand the different routes by which pharmaceuticals enter the environment;
- Be aware of strategies to reduce environmental impact of pharmaceuticals in the environment;

and be able to:

- Describe the fate of APIs in the environment in terms of their adsorption and decomposition pathways;
- Describe sub-structures in molecules that can give rise to persistence in the environment.

1. K. Kümmerer, Presence, Fate and Risks of Pharmaceuticals in the Environment, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon, L. C.

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Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 6, pp. 63-72.

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Routes into the environment

There are three main routes by which pharmaceutical molecules enter the environment, which are shown in **Figure 1:**

- Normal patient use;
- Improper disposal of unwanted pharmaceuticals and related medical devices such as patches, implants etc. into landfill or water courses;
- Point source pollution at sites of manufacture/formulation.

A fourth route which is starting to become more prevalent (or at least better detected) is the illegal or off-label use of pharmaceuticals resulting in accumulation in unintended species such as plants and animals.

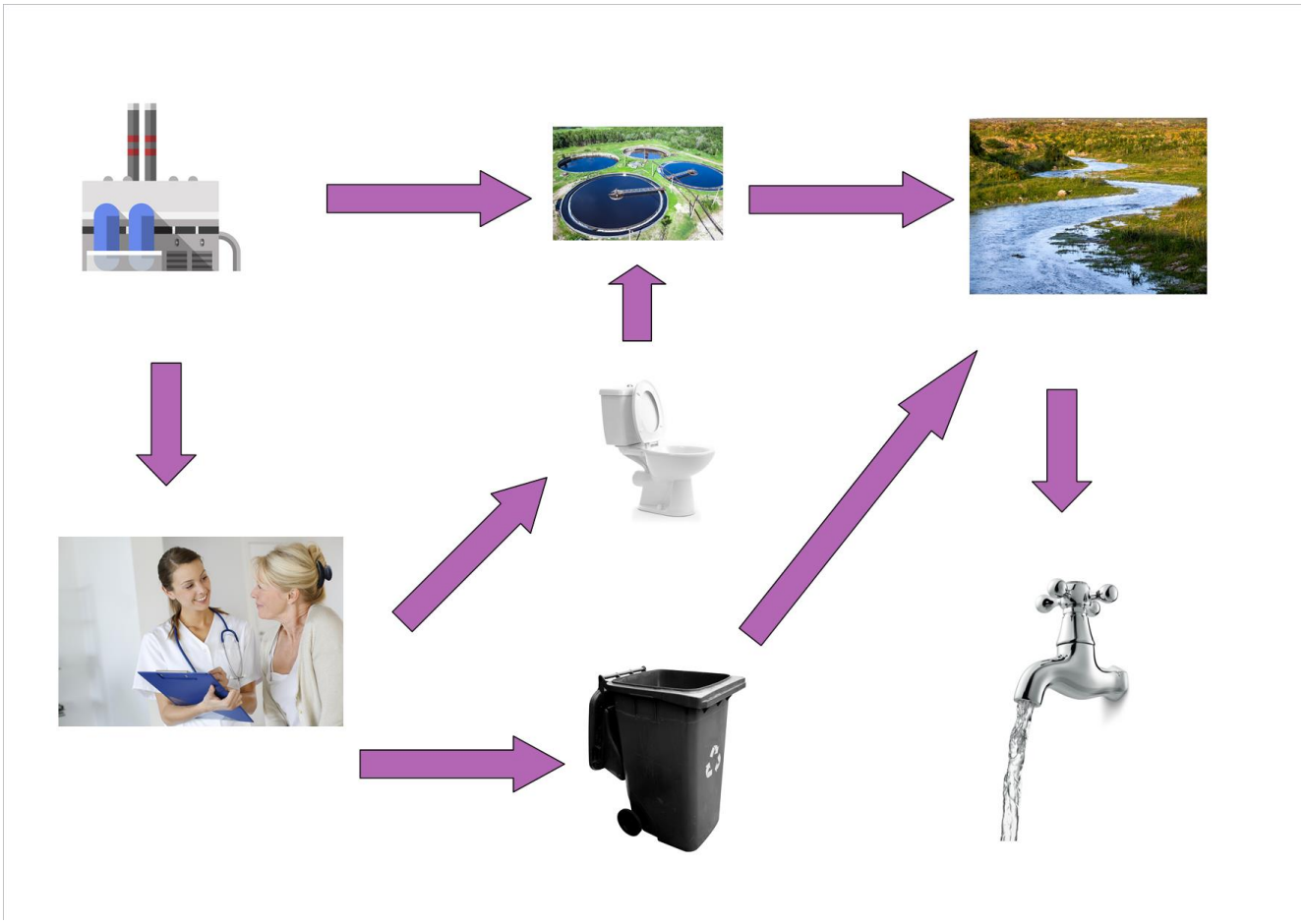

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Figure 1: ***Main routes by which pharmaceutical molecules enter the environment***

Normal patient use

After administration, the API maybe excreted unchanged in urine or faeces or metabolised to new chemical entities. An API may give a single metabolite or multiple metabolites that are excreted - these metabolites may or may not be pharmacologically active. Metabolism usually proceeds via oxidation, reduction or hydrolysis and can be followed by secondary processes such as sulphate formation, glucuronidation etc. Almost all APIs and associated metabolites have such a low vapour pressure that loss via the lungs or partition into the atmosphere from contaminated water or soil is never observed as a major route into the environment. Thus drugs and metabolites are excreted and enter into the sewage treatment system, or directly into the environment if no sewage system is in place.

Improper disposal

Improper disposal of unwanted or unused pharmaceuticals occurs via direct flushing of products into the municipal sewage system or via municipal solid waste systems, which are usually destined for landfill. Eventually APIs in landfill sites may leach out and contaminate ground water, although if blister packed or in containers, these would have to degrade first. Controlled landfill sites should collect leachate, therefore limiting this route to the environment - however, legislation governing this varies worldwide. Other solids like syringes, implants and patches improperly disposed of in landfill could also lead to API contamination of groundwater. Other improper disposal routes include the illegal landfilling or dumping into water courses of industrial waste containing API residues to avoid costs associated with proper disposal routes (land fill tax, incineration).[1] As an example, over 1,000 tonnes of unused or unwanted pharmaceuticals disposed of in Sweden in 2011. Whilst the majority (around 800 tonnes) were disposed of correctly through patient return or recycling stations, around 250 tonnes were still disposed of through home disposal.[2]

Unused medicines arise from a wide range of factors: patients not completing the prescribed course, failure to take due to undesirable side effects, out of date drugs,

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damaged packaging, and many others. It is debatable as to the extent of the escape of APIs into the environment *via* this route compared to normal patient use and point source pollution.[3]

1. S. Castensson and A. Ekedahl, Pharmaceutical Waste: The Patient Role, *Green and Sustainable Pharmacy*, 2010, 179-200.
2. Measures to reduce disposal of pharmaceuticals in distribution and health care (Last accessed: April, 2016).
3. C. G. Daughton and I. S. Ruhoy, Environmental footprint of pharmaceuticals: The significance of factors beyond direct excretion to sewers, *Environmental Toxicology and Chemistry*, 2009, **28**, 2495-2521.

Multiple choice question

1. What are the main potential means of APIs entering the environment?
    1. Excreted directly from the body
    2. Incineration
    3. Solvent/VOC loss
    4. Improper disposal
    5. Disposal in controlled landfill sites
    6. Point Source Pollution

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Areas of concern

All xenobiotic materials released through human activities have the potential to cause issues in the environment, including but not limited to pharmaceuticals. It is the fact that pharmaceuticals exhibit biological activities that has led to their consideration as an area of concern – this is especially true of antibiotics, oncology drugs and drugs exhibiting endocrine disrupting activities. For example, a number of oestrogenic residues like ethinyl estradiol (EE2) are known to be very potent and deleterious to health, but for most APIs the risk to human health is considered negligible in a high quality drinking water source.[1][2][3]The volumes of water needed to consume a single therapeutic dose of APIs present as micro-contaminants are high.[4][5] Unfortunately, access to high quality, pure drinking water is not a universal human benefit, and serious issues can arise if drinking water sources become contaminated with high levels of APIs.[6] Even for EE2, the data suggests that there will only be a risk at high point source concentrations of EE2.[7] [8]

Pharmaceuticals are a small sector of a wider chemical industry where current data on the fate and biological activity in the environment is very limited. [9] Outside of the pharmaceutical industry, some widely used industrial chemicals have been shown to have potent endocrine disruption potential (e.g. phthalates, alkylphenols) [10].

Apart from potential effects on humans, the presence of APIs in aquatic and other environments can cause undesired effects in other species – for highly active compounds like hormones and central nervous system (CNS) drugs these effects could be expected to occur at low concentration levels. It is clear that the increasing estrogenicity of water has led to issues with the feminisation of male fish, although the effects of other APIs from the CNS class are unclear.[11][12][13]

While in most cases, the scientific study and debate continues regarding the potential of harm caused by PIE, there are a number of instances where pharmaceuticals in the environment have caused well documented problems – diclofenac and the *Gyps* vultures being a notable example. At the turn of the century, a large and precipitous decline in the population of *Gyps* vulture species was noted in the Indian sub-continent, and three species are now listed as critically endangered.[14][15] This was traced to the presence of the NSAID diclofenac in the corpses of cattle and other farm animals utilised by the

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vultures as a food source. *Gyps* vultures are very sensitive to diclofenac (LD50 < 1000 µg kg^{-1}), which causes acute and lethal kidney failure. India, Nepal and Pakistan banned the veterinary use of diclofenac, but recent data suggests ~5% of animal corpses still contain high levels of diclofenac.[16]

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9. D. Taylor and T. Senac, Human pharmaceutical products in the environment – The "problem" in perspective, *Chemosphere*, 2014, **115**, 95-99.

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Multiple choice question

1. Why has there been an increasing focus on Pharmaceuticals in the Environment (PIE) in recent years?
    1. APIs are stable, therefore will not break down in the environment.
    2. New analytical methods capable of detecting molecules at lower levels have allowed us to detect previously undetected pharmaceutical residues
    3. Risk of overdosing from APIs in tap water
    4. The fate of many APIs in the environment is still largely unknown
    5. Whilst the effect of APIs on humans is known, effects on other organisms

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may not be

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Absorption and decomposition pathways

Many APIs and their metabolites once excreted from the patient or discharged into water courses are recalcitrant to further breakdown in sewage treatment plants (STPs) and natural water courses (rivers, lakes etc.). When entering the environment via the patient, APIs may be excreted unchanged, as mixtures of unchanged API alongside one or several major metabolite(s), or completely metabolised to single or mixtures of metabolite(s).

In the environment, there may be no, partial or full chemical breakdown of the excreted compounds. As with metabolites, breakdown products can be more problematic than the parent compound – potentially more toxic and more recalcitrant.[1] [2] Many APIs are not removed during typical sewage treatments, but can be adsorbed onto sewage sludge.

Therefore once released into the environment, an API or metabolite may:

- Decompose to innocuous fragments and eventually be mineralised – converted to carbon dioxide, nitrates, sulphates etc.
- Decompose to more recalcitrant fragments that are persistent.
- Be recalcitrant – i.e. does not decompose, and may or may not show undesirable biological activity.
- Bind to organic solids such as soils, river/lake sediments and sludge in STPs where it could accumulate or slowly decompose. This binding rapidly reduces the concentration of the API in solution, but may not necessarily remove it from the environment. The extent (efficiency) of binding is dependent on the nature of the solid and thus will be location dependant.

Loss to air is almost never seen for most APIs, therefore the two main environments are water (major) and land (minor).

1. M. Bergheim, R. Gminski, B. Spangenberg, M. Dębiak, A. Bürkle, V. Mersch-

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Sundermann, K. Kümmerer and R. Gieré, Recalcitrant pharmaceuticals in the aquatic environment: a comparative screening study of their occurrence, formation of phototransformation products and their in vitro toxicity, *Environmental Chemistry*, 2014, **11**, 431-444.

2. X. - H. Wang and A. Yu- Chen Lin, Is the phototransformation of pharmaceuticals a natural purification process that decreases ecological and human health risks?, *Environmental Pollution*, 2014, **186**, 203-215.

Persistence, Bioaccumulation & Toxicity (PBT)

Assessment of a chemical substance related to releases to water are based on three main properties – Persistence, Bioaccumulation & Toxicity (PBT). Any one of these properties may cause a problem, and they are often interactive: two of them together may cause significant problems. If a chemical substance is known to exhibit all three properties, then it is likely to be affected by chemical regulation. However, although compounds used in pharmaceutical production are covered under REACH, the Active Pharmaceutical Ingredient itself is exempt.[1]

- Persistence (P) – the compound is recalcitrant and not biodegraded hence will persist in the environment.
- Bioaccumulation (B) – concentration of materials from water into organisms, usually in lipids/fats. This property is very difficult and expensive to measure *in vivo* and usually the octanol/water partition coefficient (K_{OW}) is used as a surrogate indicator of bioaccumulation.
- Toxicity (T) – kills or is deleterious to microorganisms/animals. It is worth noting, however, that Endocrine Disruptor (ED) issues are more complicated: toxicity can depend on organism life stage, e.g. infancy vs adulthood. Additionally, toxicity may be indirect, making an organism more prone to infection or disease by e.g. triggering changes in DNA leading to mutation, or promoting the development of enzymes that inactivate antibiotics.[2]

1. EFPIA Management of PIE (Last accessed:).
2. E. Rahman Kabir, M. Sharfin Rahman and I. Rahman, A review on endocrine

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disruptors and their possible impacts on human health, *Environmental Toxicology and Pharmacology*, 2015, **40**, 241-258.

Decomposition routes

In the environment, there are three main decomposition routes for API molecules or their metabolites:

1) Chemical: typically, simple hydrolysis occurring between pH 5 and 8 – the pH will depend on the exact aquatic environment. Owing to the stability designed into most pharmaceutical molecules, uncatalysed chemical reactions in the environment may be limited to the hydrolysis of esters and possibly oxidation of highly reactive groups like mercaptans. Chemical transformations will not lead directly to mineralisation, but to a chemical species closely related to the original API which could be resistant to further chemical-only transformations. Most API molecules are resistant to oxidation by air, but may be oxidised in the presence of catalysts.

2) Enzymatic (or biotic degradation): molecules can be absorbed by microorganisms or higher life forms and metabolised *via* enzyme catalysis. Xenobiotic materials are metabolised to make them more polar to aid excretion, or to begin a breakdown process to utilise the molecule as a carbon/nitrogen source. These enzymatic transformations tend to follow human metabolism pathways – oxidation, reduction, hydrolysis and other less common transformations. API molecules may encounter enzyme classes common to humans but with different selectivities (such as P450s, a superfamily of haemoproteins that catalyse the metabolism of a large number of clinically important drugs), and classes of oxidative enzymes not normally utilized in human metabolism. As with humans, there can also be secondary metabolism – formation of phosphates, sulphates, and glucuronides. It should be noted that occasionally transformations in the environment can reverse the beneficial metabolic transformations in patients; one of the most problematic API molecules, EE2, is partly excreted as the soluble glucuronide which does not have estrogenic and endocrine disruption properties. This is converted back in STPs to the parent API which exhibits these undesirable properties, **Figure 1.**

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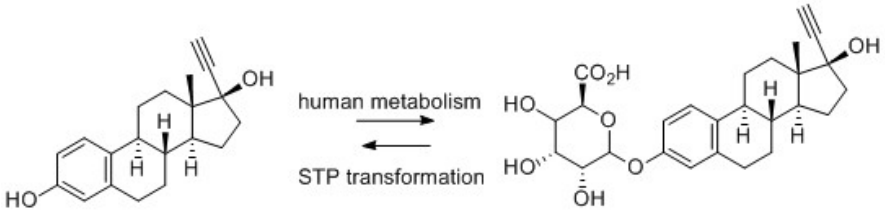

*Figure 1**: Biotic transformations of EE2***

3) Photolytic decomposition/photochemical oxidation: direct photolytic decomposition (promotion to an excited state followed by a reaction) requires absorption of natural sunlight by the molecule (e.g. has an absorption maxima >290 nm). If a molecule has a UV/Vis maximum below 290 nm, it may still be decomposed by an indirect photochemical oxidation process, through reaction with high energy species like the $ROO^{\cdot}$, $OH^{\cdot}$ radicals and singlet oxygen, which are generated photochemically *via* dissolved sensitizers based on organic substances like humic acids. (More information on photodegradation and its impact on manufacturing, packaging, storage and testing of pharmaceutical products can be found in this article).

Most APIs are degraded *in vivo via* enzyme catalysis in microorganisms or *in vitro* by direct/indirect photochemical pathways.

Multiple choice question

1. What are the main potential means of API degradation in the environment?
    1. Catalytic
    2. Enzymatic
    3. Thermal
    4. Photo-degradation
    5. Hydrolysis
    6. Oxidation by air

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Analysis of API fate

Listed below are 10 typical pharmaceutical molecules and their breakdown products under conditions likely to be encountered in the environment. A number of treatments collectively called advanced oxidation technologies/processes (AOT/AOP) can be used to treat waste water containing chemicals known to be recalcitrant and/or toxic in biological treatment/sewage treatment plants before discharge into the environment. Decomposition products from AOT/AOP processing have not been included since these technologies operate under harsh oxidative conditions that are never encountered in the environment. APIs may come into contact with milder technologies used to disinfect drinking water, which would lead to partial oxidation.

Whatever the mode of reaction, unless a molecule is mineralised, it should not be assumed that one or two transformations will render a toxic/recalcitrant molecule less so. Transformation may result in products with greater environmental issues than the original molecule.[1][2] Likewise, quantitifying the eco-toxicity of breakdown products computationally can present issues, e.g. with quantitative structure–activity relationship (QSAR) modelling since:

- It is often inaccurate for the parent pharmaceutical molecules;
- The assigned structures for the transformation products could be incorrect;
- An unambiguous answer can only be reached from physical testing.

The ten molecules have been selected to give examples of APIs across different therapeutic areas and to show examples of biotic, direct and indirect photolytic decomposition. Mainly, primary breakdown products are shown. These could be subject to further degradation processes.

1) Diclofenac

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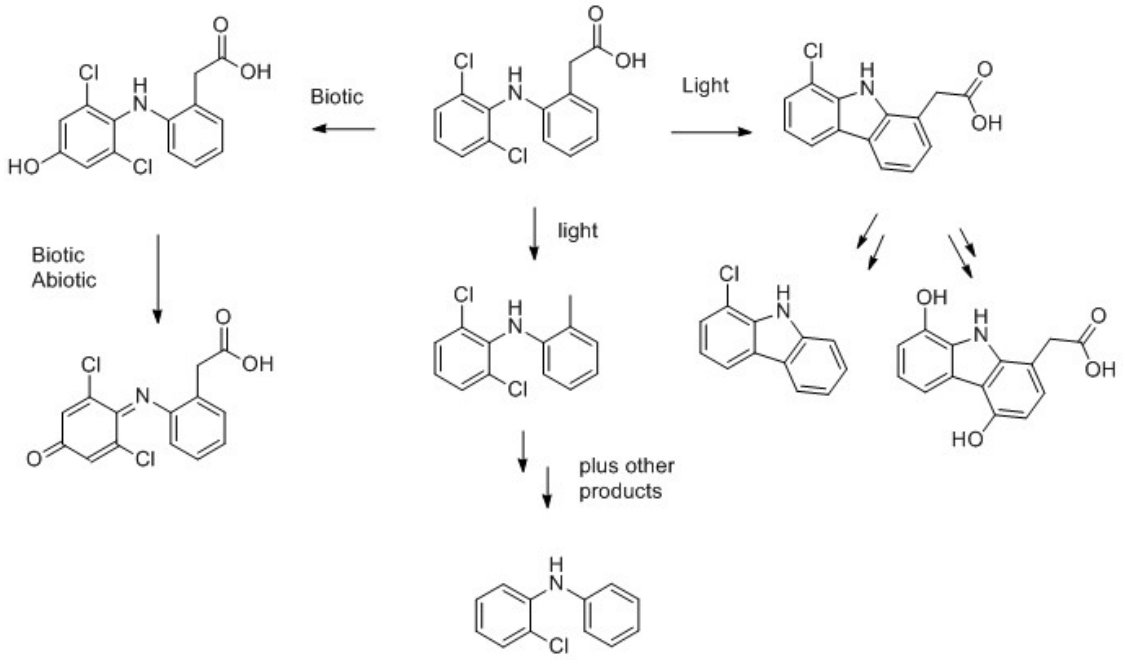

Figure 1: ***Biotic and photo-degradation routes of diclofenac*** [3] [4] [5] [6]

2) Fluoxetine

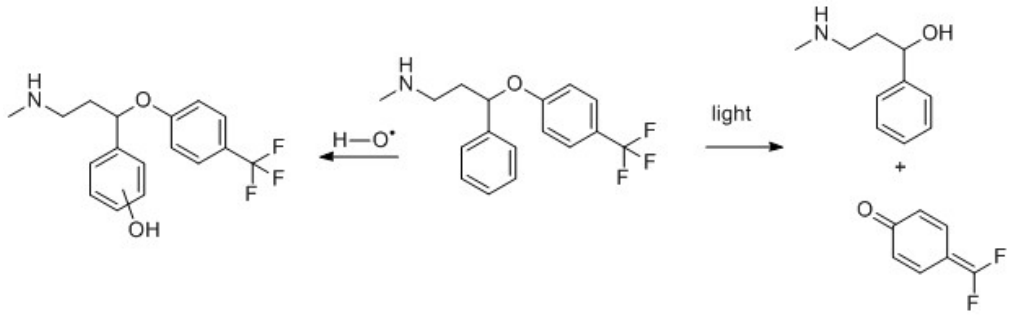

Figure 2: ***Direct and indirect photo-degrdation of Fluoxetine*** [7]

3) Paroxetine

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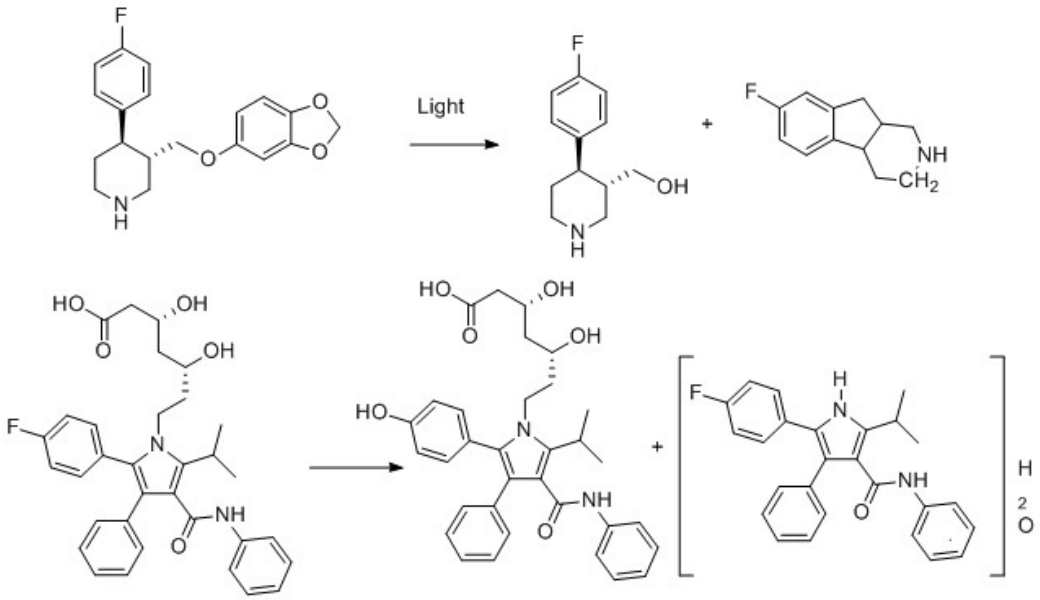

*Figure 3**: Photo-degradation of paroxetine**[8]***

4) Atorvastin

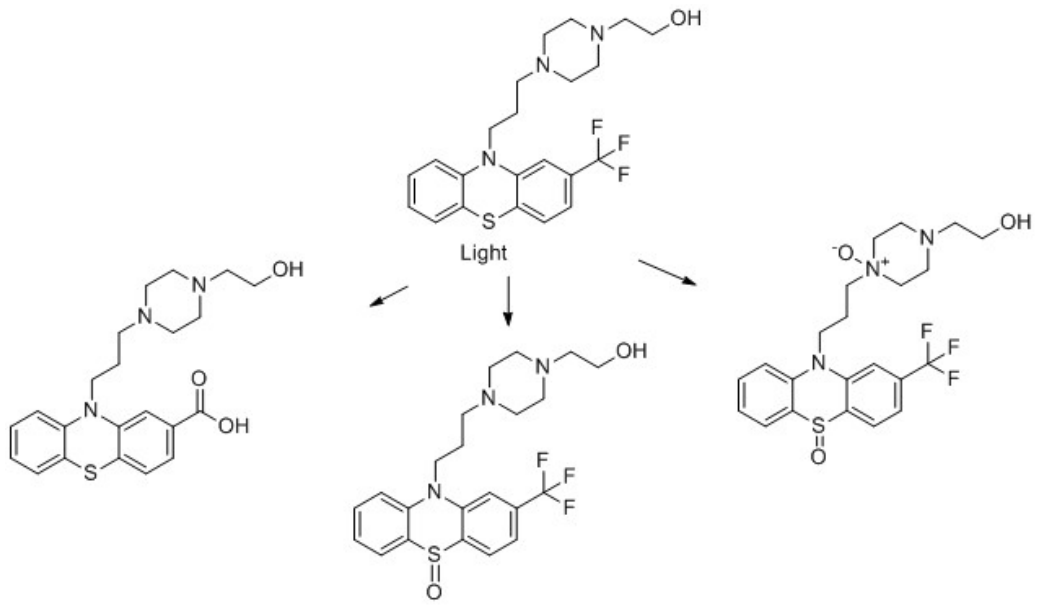

*Figure 4**: Hydrolysis of Atorvastatin**[9]***

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5) Fluphenazine

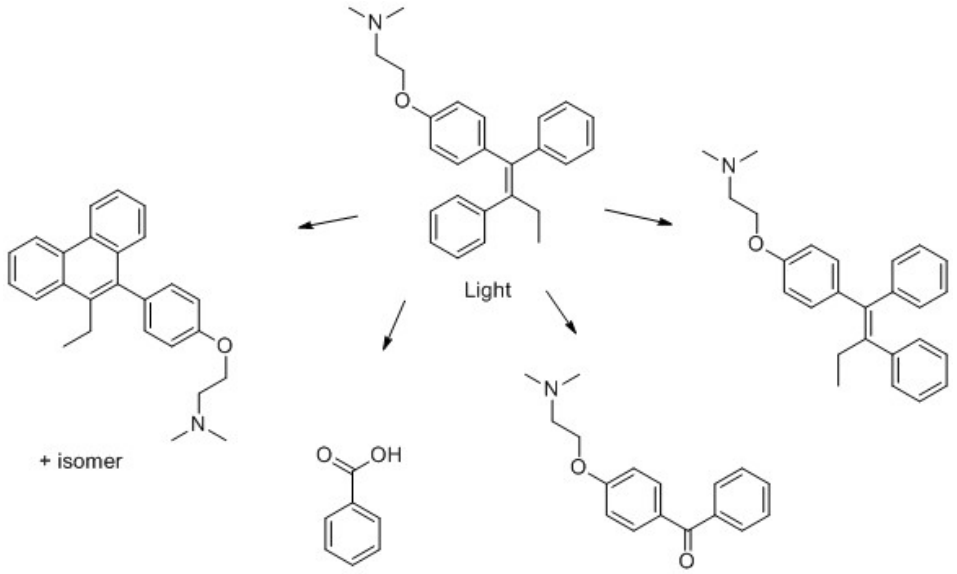
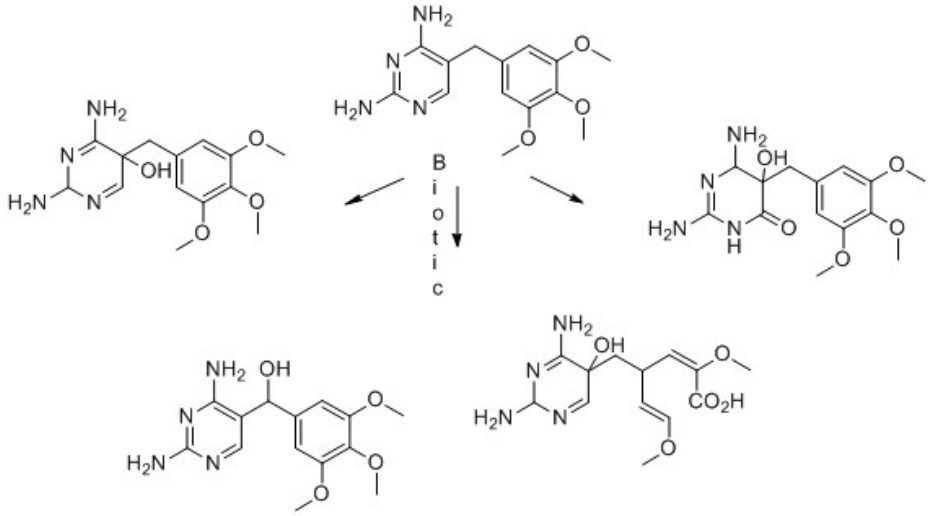


Figure 5: ***Photo-degradation of Fluphenazine*** *[10]*

6) Tamoxifen



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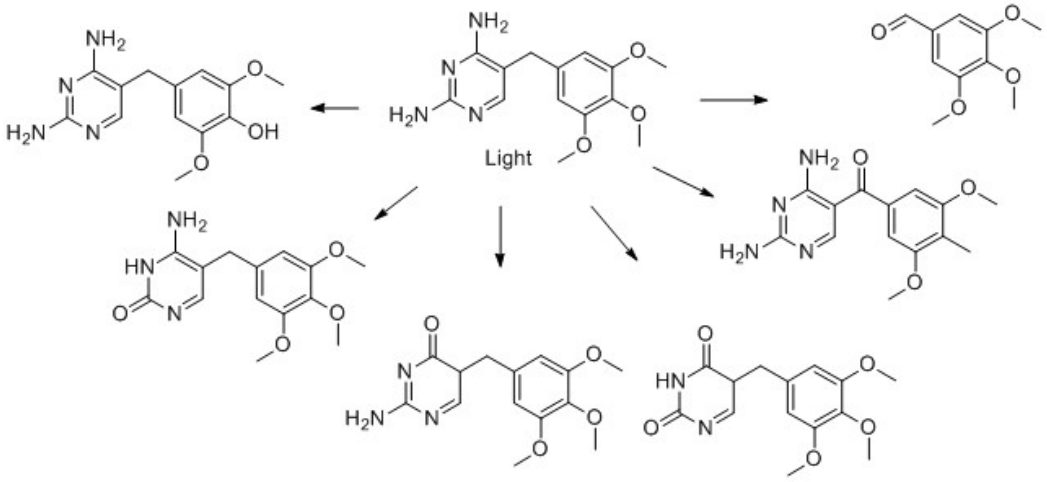

Figure 6: ***Photodegradation of Tamoxifen*** *[11]*

7) Trimethoprim

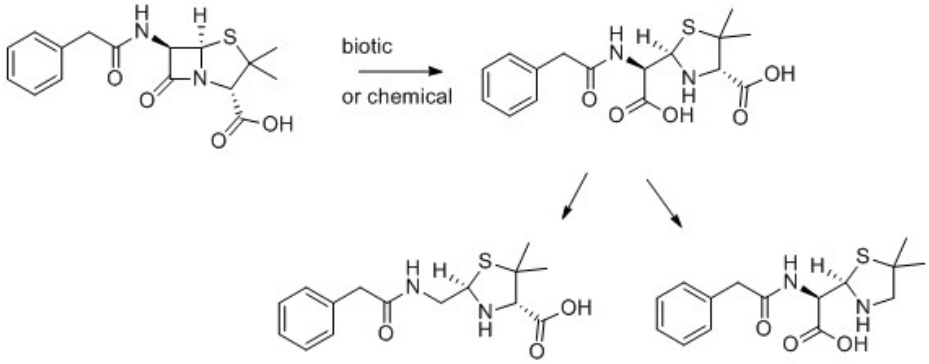

Figure 7: ***Biotic and photo-degradation of Trimethoprim*** *[12] [13] [14] [15]*

8) Penicillin G

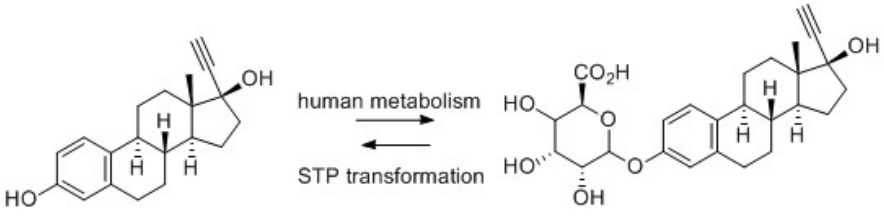

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Figure 8: ***Biotic and chemical breakdown of Penicillin G[16]***

9) Ciproflaxacin

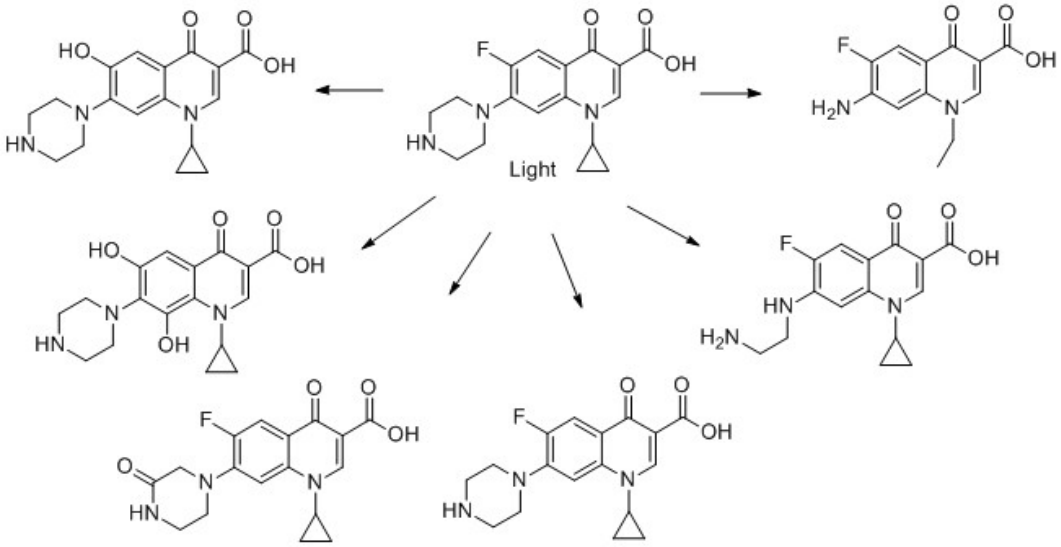

Figure 9: ***Photo-degradation of Ciprofloxacin[17] [18]***

10) Valsartan

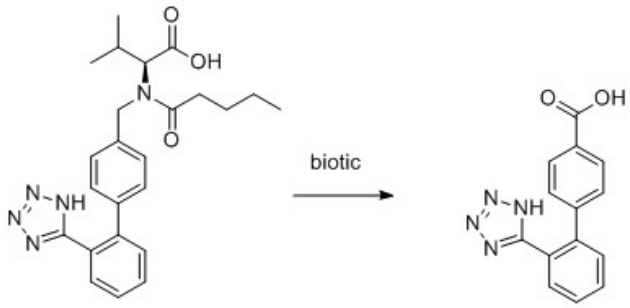

Figure 10: ***Biotic breakdown of Valsartan[19] [20]***

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Environmental Risk Assessment (ERA)

Both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) require the submission of an environmental risk assessment (ERA) with an application for a marketing license for a new pharmaceutical product. This ERA is based on a defined set of experiments designed to look at the potential effects of the API on three trophic life forms and bacteria, along with other experimentally determined/calculated figures that will give some idea of the PBT risk of the API.[1]

For some years in Sweden, data from the ERA has been made available to payers and prescribers in their database (www.fass.se). At a high level, fass.se was designed to promote the prescription of drugs with the lowest environmental fate impact, whilst ensuring that the clinical benefits are equal for the patient. Some stakeholders would like consideration of the ERA to become part of the marketing authorisation for new pharmaceutical products.[2]

The ERA for an API runs through a number of phases, involving successive levels designed to generate more data if concern around a particular substance increases. The ERA is principally based around two figures: the calculated Predicted Environmental Concentration (PEC) of the API in the environment (water) and the measured concentration at which no adverse environmental issues would be expected (Predicted No Effect Concentration - PNEC). Many ERAs and the data submitted to regulatory agencies are in the public domain[3][4][5] and can also be found by searching the FDA/EMA websites.

Many pharmaceutical companies carry out and publish studies above and beyond those needed from a regulatory requirement. The regulatory requirement focuses mainly on the fate of the API in the aqueous environment, which is where pharmaceutical residues are most likely destined.

1. European Medicines Agency Pre-Authorisation Evaluation of Medicines for Human Use (Doc. Ref. EMEA/CHMP/SWP/4447/00), Guideline on The

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Environmental Risk Assessment of Medicinal Products for Human Use (Last accessed: April, 2016).

2. B. Annonsbyrå, *National Pharmaceutical Strategy Action Plan 2014*, Ministry of Health and Social Affairs Sweden, 2014.
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5. FASS (Last accessed:).

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Multiple choice question

1. What are the criteria that are assessed to determine the environmental hazards of a molecule?
    1. Persistence, Bioavailability, Decomposition Temperature
    2. Persistence, Bioaccumulation, Toxicity
    3. Vapour Pressure, Boiling Point, Toxicity
    4. Vapour Pressure, Bioaccumulation, Decomposition Temperature
    5. Persistence, Boiling Point, Toxicity
    6. Vapour Pressure, Bioaccumulation, Toxicity

Answers on last page

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Summary and further reading

Further information on the mechanisms and pathways of API breakdown in the environment are provided in a number of comprehensive reviews on the fate of API molecules in the environment and are provided in the recommended reading below.

Recommended reading:

K. Kümmerer, Presence, Fate and Risks of Pharmaceuticals in the Environment, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 6, pp. 63-72.

T. Haddad, E. Baginska and K. Kümmerer, Transformation products of antibiotic and cytostatic drugs in the aquatic cycle that result from effluent treatment and abiotic/biotic reactions in the environment: An increasing challenge calling for higher emphasis on measures at the beginning of the pi, *Water Research*, 2015, **72**, 75-126.

A. Barra Caracciolo, E. Topp and P. Grenni, Pharmaceuticals in the environment: Biodegradation and effects on natural microbial communities. A review, *Journal of Pharmaceutical and Biomedical Analysis*, 2015, **106**, 25-36.

J. K. Challis, M. L. Hanson, K. J. Friesen and C. S. Wong, A critical assessment of the photodegradation of pharmaceuticals in aquatic environments: defining our current understanding and identifying knowledge gaps, *Environmental Science: Processes & Impacts*, 2014, **16**, 672-696.

I. K. Konstantinou, D. A. Lambropoulou and T. A. Albanis, Photochemical Transformation of Pharmaceuticals in the Aquatic Environment: Reaction Pathways and Intermediates, in *Xenobiotics in the Urban Water Cycle* , D. Fatta-Kassinos, K. Bester and K. Kümmerer, Springer Netherlands, 2010, ch. 10, vol. 16, pp. 179-194.

M. D. Celiz, J. Tso and D. S. Aga, Pharmaceutical metabolites in the environment: analytical challenges and ecological risks, *Environmental Toxicology and Chemistry*, 2009, **28**, 2473-2484.

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K. Kümmerer, Pharmaceuticals in the Environment, *Annual Review of Environment and Resources*, 2010, **35**, 57-75.

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Quiz answers

Routes into the environment - Multiple choice question

1. What are the main potential means of APIs entering the environment?
   ***Correct answers**:*
   - *(u'Excreted directly from the body',)*
   - *(u'Improper disposal',)*
   - *(u'Point Source Pollution',)*

Areas of concern - Multiple choice question

1. Why has there been an increasing focus on Pharmaceuticals in the Environment (PIE) in recent years?
   ***Correct answers**:*
   - *(u'New analytical methods capable of detecting molecules at lower levels have allowed us to detect previously undetected pharmaceutical residues',)*
   - *(u'The fate of many APIs in the environment is still largely unknown',)*
   - *(u'Whilst the effect of APIs on humans is known, effects on other organisms may not be',)*

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