Pharmaceuticals and Personal Care Products in the Environment: What are the Big Questions?


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**Running title:** PPCPs in the environment
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ABAB, PCD, AC, JPS and TV have provided consultancy services to the PPCP industry. DJC, SEB, SDD, JFE, TG, FM, JOS, JPS, RMS, RDM are employed by the PPCP sector. ABAB, MVK, PCD, AC, FG, DGJL, JML, JLP, BWB, KC, JPG, PKS, JPS, GVDK, MEM, MRS, ET, VLT, GRT or TV have received funding from either industry or government or both of these for research on PPCP issues. MAR, DJC, SEB, RDM, PCD, FM, JRS, RMS have shareholdings in the PPCP sector. All other authors declare they have no competing financial interests.
Abstract

OBJECTIVE: Over the past 10-15 years, a substantial amount of work has been done by the scientific, regulatory and business communities to elucidate the effects and risks of pharmaceuticals and personal care products (PPCPs) in the environment. This review was undertaken to identify key outstanding issues regarding the effects on human and ecological health in order that future resources will be focused on the most important areas.

DATA SOURCES: The ‘key question’ approach was used to identify the principle issues that need to be addressed in order to better understand and manage the risks of PPCPs in the environment. Initially, questions were solicited from academic, government and business communities around the globe. A list of 101 was then discussed at an international expert workshop and a top 20 list was developed. Following the workshop, workshop attendees ranked the 20 questions by importance.

DATA SYNTHESIS: The top 20 priority questions fell into seven categories: 1) prioritisation of substances for assessment; 2) pathways of exposure; 3) bioavailability and uptake; 4) effects characterization; 5) risk and relative risk; 6) antibiotic resistance; and 7) risk management.

CONCLUSIONS: A large body of information is now available on PPCPs in the environment. This exercise has prioritized the most critical questions to aid in development of future research programs on the topic.
Introduction

Pharmaceuticals and personal care products (PPCPs) include numerous chemical classes. Pharmaceuticals are used primarily to prevent or treat human and animal disease, whereas personal care products are used to improve the quality of daily life and include products such as moisturizers, lipsticks, shampoos, hair colors, deodorants and toothpastes. Human use PPCPs are generally excreted and emitted to the sewerage system following use. The compounds may then be released to surface waters or enter terrestrial systems when sewage effluent is used for irrigation or where sewage sludge is applied, as a fertiliser, to agricultural land (Kinney et al. 2006; Ternes et al. 2004). Veterinary pharmaceuticals are released to the environment either directly, from use in aquaculture and the treatment of pasture animals, or indirectly during the land application of manure and slurry from livestock facilities (Boxall et al. 2003a). PPCPs may also be released to the environment from manufacturing sites (Fick et al. 2009).

A range of PPCPs has been detected in the natural environment across the world (e.g., Hirsch et. al. 1999; Kolpin et al. 2002; Ramirez et al. 2009). While reported concentrations are generally low, many PPCPs have been detected across a variety of hydrological, climatic and land-use settings and some can persist in the environment for months to years (e.g., Monteiro and Boxall 2009). Pharmaceuticals, and a handful of chemicals used in personal care products, are biologically active compounds that are designed to interact with specific pathways/processes in the target humans and animals. Concerns have therefore been raised over the potential effects of active PPCPs in the environment on human and environmental health and, over the past 15 years, a substantial amount of work has been done to determine the occurrence, fate, effects and risks of PPCPs in the environment. There have also been regulatory developments around the assessment of the risks of PPCPs in the environment (e.g. CDER 1998; CHMP 2006, 2008; ECETOC 2008; VICH 2000, 2004; WHO 2011).
Attempts have been made to synthesise the wealth of knowledge gained to date and to identify the remaining major research gaps and gaps in regulation (e.g. KNAPPE 2008). However, these exercises have tended to focus on select regions of the world as well as established markets and have not always engaged fully with major stakeholder groups.

One approach to identifying key issues in a topic area is to perform a ‘Key Question Exercise’ which is designed to promote engagement of researchers and stakeholders from a broad range of sectors (e.g., Fleishman et al. 2011; Rudd et al. 2011). The exercises begin with an initial solicitation of interested parties to develop a list of questions that individual members of the community feel are important on a particular topic. A workshop is then held to discuss and prioritise the questions raised and to develop a final list (e.g. 20, 40 or 100). In this paper we report the results of a Key Question exercise that was performed to identify and rank the top 20 questions relating to the hazards, exposure assessment and environmental and health risks of PPCPs in the natural environment. A description of the approach used and the full list of submitted questions is provided in the Supplemental Material.

**Top 20 Questions**

The top 20 questions, described below, fell into seven categories: 1) prioritisation of PPCPs; 2) pathways of exposure; 3) bioavailability and uptake; 4) effects characterization; 5) risk and relative risk; 6) antibiotic resistance; and 7) risk management.

**Prioritization of PPCPs**

*What approaches should be used to prioritize PPCPs for research on environmental and human health exposure and effects?* Over 4000 pharmaceuticals are currently in use and a great variety of chemicals are used in personal care products. It would be impossible to experimentally assess the hazards and risks of all of these in a timely manner. Prioritization
approaches can be used to focus monitoring, testing and research resources and to identify those PPCPs that are likely to pose the greatest risk in a particular situation. A number of prioritization methods have been proposed for, and applied to, human pharmaceuticals (e.g., Kostich and Lazorchak 2007; Kostich et al. 2010; Sanderson et al. 2004) and veterinary medicines (Boxall et al. 2003b; Capelton et al. 2006; Kools et al. 2008). Many of these approaches use exposure and toxicological predictions or information on pharmaceutical potency so they can be readily applied to large numbers of compounds. These approaches should be further developed for different situations covering different geographical regions, climates, demographics and cultural backgrounds and should be designed in such a way that they account for the use practices, complex fate processes and the specific modes of action associated with many PPCPs.

Pathways of Exposure

What are the environmental exposure pathways for organisms (including humans) to PPCPs in the environment and are any of these missed in current risk assessment approaches? PPCPs can enter the environment by a number of pathways (Figure 1). Regulatory environmental risk assessment approaches for PPCPs consider releases to surface waters from wastewater treatment systems, aquaculture facilities, and runoff from fields and releases to soils during biosolid and manure application (e.g. CHMP 2006; CVMP, 2008; Price et al. 2010). Other exposure pathways exist, including emissions from the manufacturing sites (Fick et al. 2009), disposal of unused medicines to landfills, runoff of veterinary medicines from farmyard hard surfaces, irrigation with wastewater, off-label emissions and disposal of carcasses of treated animals. Management and use practices in different regions of the world can also vary, so an important exposure pathway in one geographical area may be a less important pathway in another region. For example, in several
regions of the world the connectivity of the population to wastewater treatment technologies is limited so regulatory exposure modelling, based on European and N. American systems, will not always be relevant. An understanding of the release mechanisms and dominant exposure pathways for PPCPs in different regions is therefore needed.

**Bioavailability and uptake**

**How can the uptake of ionizable PPCPs into aquatic and terrestrial organisms and through food chains be predicted?** A significant proportion of PPCPs are ionizable substances. While methods are available for estimating uptake of ionisable compounds into fish and invertebrates (e.g. Fu et al. 2009; Meredith-Williams et al., 2012), our understanding of the factors and processes influencing uptake of PPCPs from different environmental compartments into organisms is still less well developed than for non-ionizable chemicals (Brooks et al. 2009). The uptake of ionisable PPCPs is also very sensitive to changes in environmental conditions such as pH and soil and sediment characteristics. Data on uptake through food chains is almost non-existent. Future work should therefore focus on understanding the uptake routes for PPCPs from a range of matrices into single organisms and food webs covering different traits (e.g. size, life cycle characteristics, method of respiration). Based on these studies, improved models for estimating uptake of ionisable PPCPs into organisms and through food chains should be developed.

**What is the bioavailability of non-extractable residues of PPCPs?** Many PPCPs dissipate rapidly in animal manures, biological treatment processes, soils and sediments. Data from degradation studies with radiolabelled PPCPs indicate that in many instances, the observed dissipation can be due to the formation of non-extractable residues (NERs; e.g. Kreuzig and Holtge 2005). NERs are defined as species of a chemical that cannot be extracted from a matrix (sediment, soil etc.) by methods which do not significantly change the chemical nature
of the residues. In general, the chemical identities of these NERs are unknown and concerns have been raised that the NERs may in the future become bioavailable as manure and biosolid material is broken down following addition to soils, or due to changes in agricultural practices or environmental changes such as changes in the pH or ionic strength of a system (Barraclough et al., 2005; Gevao et al., 2000). The challenge is to demonstrate whether NERs for PPCPs are bioavailable or whether they are likely to become bioavailable. This is a challenge not only for PPCP risk assessment but also for other classes of chemicals, including pesticides (e.g. Calderbank 1999; ECETOC 2010).

Effects characterization

How can pharmaceutical preclinical and clinical information be used to assess the potential for adverse environmental impacts of pharmaceuticals? A lot of information is available on the behaviour and effects of pharmaceutical active ingredients from mammalian studies and clinical trials. The pharmaceutical industry also devotes significant resources to collating new and emerging data as part of their post-authorization pharmacovigilance programmes. Several epidemiological studies have also been performed to explore the potential long-term health effects of pharmaceuticals on workers in the pharmaceutical industry (e.g., Heron and Pickering 2003). On the other hand, comprehensive information on fate and effects in the environment is still only publicly available for a small percentage of pharmaceuticals and, with a few exceptions (e.g. the UK Veterinary Medicines Directorate Suspect Adverse Reactions Reporting Scheme), pharmacovigilance programs do not consider environmental effects. By accessing the wealth of data from mammalian studies and clinical trials and building upon the advanced methods for predicting long-term low level effects arising from occupational exposure, it may be possible to establish whether low levels of a
pharmaceutical in the environment constitute a threat to environmental and human health or not (Ankley et al. 2007, Berninger and Brooks 2010; Huggett et al. 2003; Seiler 2002).

**What can be learned about the evolutionary conservation of PPCP targets across species and life stages in the context of potential adverse outcomes and effects?** Most pharmaceuticals, and a few personal care products, are designed to interact with a target (such as a specific receptor, enzyme or a biological process) in humans and animals in order to deliver the desired therapeutic effect. If these targets are present in organisms in the natural environment, it is possible that exposure to some PPCPs will elicit effects on those organisms. Knowledge on the presence or absence of PPCP targets across a wide range of taxa could, therefore, be invaluable in identifying: 1) PPCPs that might affect the environment at low concentrations; and 2) those organisms and life stages of organisms that are most likely to respond to exposure to a particular pharmaceutical (Ankley et al. 2007; ECETOC 2008; Gunnarsson et al. 2008; Huggett et al. 2003; Seiler 2002; Trudeau et al. 2005). Comparative biochemistry, genomics and other ‘omic’ technologies offer potential tools for identifying PPCPs of potential concern as well as the most sensitive and vulnerable species.

**How can ecotoxicological responses, such as histological and molecular-level responses, observed for PPCPs, be translated to traditional ecologically important endpoints such as survival, growth and reproduction of a species?** This is a question that is relevant to many other classes of environmental contaminants (Huggett et al. 1992). A range of responses has been seen in organisms exposed to PPCPs, including histological changes, effects on behaviour, biochemical responses and up or down regulation of genes (Ankley et al. 2007; Brooks et al. 2009; Corcoran et al. 2010). These responses are generally not considered in current risk assessment schemes but can occur at concentrations orders of magnitude lower than concentrations where effects are observed in regulatory tests such as acute studies.
looking at effects on fish and invertebrate mortality or chronic studies looking at effects on reproduction and growth (Figure 2). The importance of these responses in terms of survival of populations and ecosystem functioning is poorly understood. However an understanding of these relationships is necessary in order to know the broader implications of the non-standard observations on ecosystem health and, to determine the benefits of incorporating data from non-standard responses into prospective and retrospective risk assessment frameworks. As we understand the effects of PPCPs in humans so well, from the molecular to whole organism level, PPCPs may provide a unique opportunity to develop an understanding of the relationships between molecular, cellular and whole organism endpoints in the natural environment.

**How can ecotoxicity test methods, which reflect the different modes of actions of active PPCPs, be developed and implemented in customized risk assessment strategies?** Existing risk assessment approaches for PPCPs in Europe and North America employ standard OECD test methods for examining effects on organisms (CDER 1998; CHMP 2006, VICH 2000, 2004). Some authorities can ask for non-standardised studies where a risk cannot be ruled out based on standard tests. Concerns have been raised over whether the standard methods will identify ecologically important effects of specifically acting PPCPs (Brooks et al. 2009; ECETOC 2008). The effect of the non-steroidal anti-inflammatory compound, diclofenac, on vulture populations (Oaks et al., 2004) provides an illustration of an endpoint that would not have been predicted from standard studies. Further research is required to understand the potential effects of PPCPs with different modes of action on aquatic and terrestrial organisms and, if appropriate, guidance is required on which testing approaches (species and endpoints) could be employed in the risk assessment process. It would be short sighted however to reduce testing strategies totally to methods that reflect specific modes of action as unexpected
effects in organisms can occur as illustrated by the high potency of the selective serotonin reuptake inhibitor, fluoxetine, to algae (Oakes et al., 2010).

**How can effects from long-term exposure to low concentrations of PPCP mixtures on non-target organisms be assessed?** Aquatic and terrestrial systems will be exposed to a complex mixture of PPCPs and other contaminants. Many pharmaceuticals, if consumed together at therapeutic doses, can cause severe adverse interactions in humans (e.g. Juurlink et al., 2003). If aquatic organisms respond to these compounds in the same way as humans, it is possible that effects on the environment could be greater than predicted based on effects data for the single compounds. Antimicrobial PPCPs, may also increase persistence of other PPCPs thus affecting the overall risk (Monteiro and Boxall, 2009). Many human use PPCPs will be emitted continuously to the environment so organisms in the environment will be exposed throughout their lifetime. However, no regulatory program for prospective environmental risk assessment of PPCPs (or other product classes) considers the long-term combined toxicity of mixtures of chemicals so there is a need to develop new approaches for assessing the risks arising from long-term exposure to mixtures. The concept of mixture risk assessment is gathering momentum, particularly in the public health arena and recent reports by the European Commission, the UK Committee on Toxicology and US National Academy of Sciences have already started to consider this topic (e.g. Kortenkamp et al. 2009). For human medicines, it may be possible to use the observations of contra-indications in humans to provide an indication of whether a particular combination of pharmaceuticals in the environment may be of concern. Mixture interactions could also be simulated by pharmacokinetic modelling, linking models at the interaction site (Krishnan, et al., 2002), although this will require extensive quantitative information on pharmacokinetics and/or toxicokinetics. The use of *in vitro* assays for relevant endpoints (e.g., carcinogenic, mutagenic and reproductive effects) to assess the effects of mixtures of pharmaceuticals that
typically occur in environmental systems may also provide useful information for use in risk assessment, although these will need to be extensively validated before use.

**Can non-animal testing methods be developed that will provide equivalent or better hazard data compared to current in vivo methods?** For personal care products, there is regulatory pressure in some geographic regions to reduce the amount of animal testing used for human safety and environmental risk assessment in a 3R’s framework (reduce, refine, replace). It may be possible to reduce the amount of animal testing using non-animal testing methods such as *in vitro* approaches and *in silico* methods, (e.g., quantitative structure-activity relationships, read-across and expert systems), by optimizing experimental designs, and employing intelligent testing strategies (Hutchinson et al. 2003; OECD 2010; Rufli et al. 2011). While these approaches are being promoted (e.g. National Academy of Sciences 2007) and used for industrial chemicals (e.g., as part of the REACH regulations in Europe and elsewhere (Halder et al. 2011)), additional approaches are needed to replace animal test methods considering those with specific and non-specific modes of action.

*Risk and relative risks*

**How can regions where PPCPs pose the greatest risk to environmental and human health, either now or in the future, be identified?** Risks of PPCPs in the environment in different geographic regions will vary due to differences in the presence/absence and type of manufacturing sites, level of PPCP use, population demographics, cultural practices, environmental and climatic characteristics, dilution potential of receiving environments and infrastructure related to wastewater and drinking water treatment. Risks may change in the long term due to factors such as increased urbanization and effluent-dominated instream flows (Brooks et al. 2006), increased disease pressures, demographic change, population increases, technological developments (e.g. move from small molecules to biologics,
development of nanomedicines and improvements in drug delivery) and climate change. By better understanding the drivers for PPCP exposure in different regions, it may be possible to identify those areas that are at greatest risk, meaning that control options can be focused to areas/regions where they will be most effective. By understanding how risks will change in the longer term, it may be possible to anticipate and pre-emptively mitigate against unacceptable changes in risks.

How important are PPCPs relative to other chemicals and non-chemical stressors in terms of biological impacts in the natural environment? PPCPs will be released to the natural environment along with many other chemicals (e.g., nutrients, metals, industrial chemicals, pesticides and natural hormones). The natural environment will also be exposed to non-chemical stressors such as changes in water flow and temperature. The affect of PPCPs could be small compared to the many other chemical and non-chemical stressors present in the natural environment. In order to make informed management decisions, an understanding of the relative impact of PPCPs compared to other pressures in a particular situation is needed.

Do PPCPs pose a risk to wildlife such as mammals, birds, reptiles and amphibians? Most studies have focused on effects of PPCPs on fish and invertebrates and our knowledge of risks to other wildlife species, such as birds and small mammals, is less developed. Several case studies highlight the importance of understanding effects on birds and mammals. For example, the inappropriate use of diclofenac and associated cultural practices regarding disposal of animal carcasses, combined with the high sensitivity of vultures to diclofenac, were responsible for the decline in populations of three vulture species in Asia (Oaks et al. 2004) resulting in ecological, socio-economic, cultural and human health impacts (Markandya et al. 2008). Indirect effects on top predators may also be important; for example there is concern that antiparasitic veterinary medicines may be indirectly affecting populations of insect-eating bats and birds by affecting the quantity of the food resource.
available (McCraken 1997). More work is needed to better understand the exposure of birds, mammals and amphibians to PPCPs as well as the potential toxicological effects of PPCPs on these species.

**How can the environmental risks of metabolites and environmental transformation products of PPCPs be assessed?** Pharmaceuticals may be metabolised in the treated human or animal so a mixture of parent compound and metabolites will be released to the environment. Transformation of PPCPs will also occur in wastewater treatment processes, surface waters, sediments, manure, soils and drinking water treatment processes (Escher and Fenner 2011). While metabolites and transformation products are usually less hazardous than the parent compound, data for pesticides indicates that some can be more toxic (Sinclair and Boxall 2003). The environmental fate of these substances can also be different from the parent compound, meaning that environmental compartments that are not exposed to the parent may be exposed to a transformation product (Boxall et al. 2004). Concerns have also been raised over the potential human health effects of selected transformation products of PPCPs such as the halogenated and nitrosamine products resulting from transformation in wastewater and drinking water treatment processes (Sedlak and von Gunten 2011). We need to better understand the release and formation of transformation products of PPCPs in the environment and develop approaches for identifying transformation products that could pose a greater risk than the parent compound.

**How can data on the occurrence of PPCPs in the environment and on quality of ecosystems exposed to PPCPs be used to determine whether current regulatory risk assessment schemes are effective?** Environmental risk assessments for PPCPs have been required in Europe and North America for some time. The effectiveness of these prospective risk assessment approaches, in terms of predicting exposure and effects in the ‘real world’, is not always clear. By bringing together data on the occurrence of PPCPs in different regions
as well as information on the status of biological communities and ecosystems, it may be possible to establish whether environmental risk assessment schemes really work for PPCPs. It is important to recognize, that this is a general issue relevant to other classes of chemicals that require an environmental risk assessment. The application of eco-epidemiological approaches that link chemical pressures to effects on ecosystems (e.g. De Zwaart et al., 2006) may help answer this question.

**Antibiotic resistance**

*Does environmental exposure to PPCP residues result in the selection of antimicrobial resistant micro-organisms and is this important in terms of human health outcomes?* The World Health Organization (WHO 1998) has identified the emergence of antimicrobial resistance as one of the serious concerns of health policies in the future. One of the major concerns relating to the occurrence of antibiotic compounds in the environment is the potential for selection of resistant microbial species. Antibiotics in the environment may enhance the formation of single, cross- and multiple resistance in bacteria (e.g. Byrne Bailey et al. 2008; Gaze et al., 2011; Knapp et al. 2010; Kristiansson et al. 2011). However, the role of environmental residues of antibiotics in the selection of antibiotic resistance is still unclear and, even where information exist, it is only available for a few antibiotics (e.g. sulfonamides and fluoroquinolones). There is an urgent need to better understand the importance of residues of antibiotics in the environment as a pressure for selecting for antibiotic resistance and the potential for the acquired resistance to transfer to human and animal pathogens and thus affect human health. This assessment must be interpreted against the backdrop of antibiotic resistance (the ‘resistome’) naturally found in the environment or caused by inappropriate clinical use of antibiotics or by other environmental contaminants.
How can the risks to human health, arising from antibiotic resistance selection by PPCPs in the natural environment, be assessed? Current regulatory paradigms do not consider the potential for antibiotic resistance selection in soils and surface waters. In the event that the occurrence of antibiotics in the natural environment is demonstrated to be an important driver for resistance selection, it may be necessary to develop approaches for considering resistance selection as an endpoint in the safety assessment of new antibiotic substances. There is also a need to understand the extent to which feces from treated animals and humans act as an environmental source of resistant microorganisms and associated genetic elements.

Risk management

If a PPCP has an adverse environmental risk profile what can be done to manage and mitigate the risks? In the event that a PPCP is found to pose an unacceptable risk to the environment, options exist for minimising or removing emissions to the environment, including: substitution with more environmentally benign compounds; the development of better drug delivery systems meaning that smaller doses are needed; the use of improved packaging and package sizes to extend shelf life and reduce the amount of a product that expires and must be discarded unused; changes in prescription and animal husbandry practices; and the introduction of improved wastewater treatment options (e.g., Daughton 2003a and b; START 2008). The efficacy and practicality of many of the solutions is, however, poorly understood. A systematic study to understand the benefits of different management and mitigation options and any societal and environmental costs associated with a particular option in different regions of the world is needed. This will allow informed decisions to be made on the best mitigation strategy.

What effluent treatment methods are effective in reducing the effects of PPCPs in the environment while at the same time not increasing the toxicity of whole effluents? During
biological treatment some PPCPs may be degraded or removed through sorption to sludge (Prasse et al. 2011; Ternes et al. 2004). Recalcitrant PPCPs may be removed using tertiary treatment methods such as ozonation, activated carbon adsorption or nanofiltration (Ternes et al. 2004). In some cases, the wastewater treatment process may increase the risk. For example, ozonation may result in the formation of more toxic oxidation products. In other cases, the introduction of a treatment option may move the exposure from one environmental compartment to another. For example, introduction of procedures to enhance sorption of PPCPs to activated sludge treatment will mean that while emissions to water bodies are reduced, exposure of the terrestrial environment will increase when the sludge is applied to soils as a fertiliser (McClellan and Halden 2010). Increased knowledge is required to determine the effectiveness and consequences of waste and drinking water treatment options on PPCP fate and effects.

**How can the efficacy of risk management approaches be assessed?** The introduction of risk management strategies can result in environmental, economic and societal costs. In these cases, management options should be shown to be effective at reducing environmental impacts before they are widely introduced. Guidance is needed on environmental monitoring approaches to demonstrate the efficacy of a particular management option. These approaches should not only include monitoring of changes in the occurrence of a particular substance but also be able to monitor changes (improvements) in the health of the ecosystem of interest. The costs (economic, social and environmental) of a management option will also need to be considered. For antimicrobial compounds, it is possible that control options (e.g., banning of antibiotic substances as growth promoters and/or prophylactic treatments in agriculture) will not be effective in controlling antibiotic resistance, as once antibiotic resistance genes are present in the environment they may not disappear. Other anthropogenic compounds will also
facilitate the selection of microorganisms that are resistant to some classes of antibiotic (e.g. Gaze et al., 2006).

**Ranking of questions and next steps**

When questions were ranked in terms of importance, the question relating to the relative risks of PPCPs compared to other environmental stressors was identified as the most important (Table 1). This reflects the significance of the question for allocation of future research resources and the implementation of future policy developments and risk management options. If the answer is that PPCPs are important stressors compared to others stressors in the environment, then many other questions identified in this exercise will be relevant and important. However, if the answer to this question is that PPCPs pose relatively minor risks compared to other stressors in the environment, then expending large amounts of resources answering the other questions may not offer the best use of resources in terms of global environmental protection. Questions around prioritisation, improved characterisation of effects and antibiotic resistance were also ranked highly while questions around risks of non-extractable residues, treatment and the use of non-animal studies were ranked lower (Table 1). For each question, potential approaches that could be adopted to address the question were identified. We envisage that this information will be invaluable in formulating future research programmes around the risks of PPCPs in the environment.

It is important, in the development of future research and policy initiatives, to recognise that many of the questions are inter-related and that knowledge gained from one question may be needed to address other questions (Table 1). In some instances, it may be necessary to address a lower ranked question before a high ranked question can be fully answered. For example, knowledge gained from answering questions around prioritisation of PPCPs, the importance of the environment as a selection pressure for antimicrobial resistance,
identification of regions of greatest risk and characterisation of risks to wildlife may all need to be answered before the top ranked question can be addressed. The level of challenge associated with answering a question also varies (Table 1). Questions around the risks of non-extractable residues and prioritisation of PPCPs may be addressable with limited investment over relatively short timescales compared to other questions.

Many questions (e.g. the questions around NERs, mixture interactions and extrapolation of results on molecular and cellular effects to ecologically relevant endpoints) are not unique to PPCPs so it may be appropriate to address these in broader research programmes looking at other chemical classes. However, the detailed understanding that we have for the effects of many PPCPs on humans might make them good candidate ‘model’ compounds for addressing some of these wider questions.

**Wider global relevance of the exercise**

It is important to recognise that while participants from different regions of the world were engaged in the exercise, the majority of question submissions (92%) were from North America (46.6%), Europe (29.8%) and Australia/New Zealand (15.5%). The workshop was also dominated by North American (51%) and European attendees (14.6%) and representatives of multi-national corporations (34%). To begin to determine whether the workshop conclusions were widely relevant to the global PPCP community, two subsequent regional workshops were held in S. Korea and Australia in order to determine the relevance of the 20 questions to the E. Asian and Australia/New Zealand regions and to identify additional questions that may be important to these regions. The conclusions of these workshops will be presented in detail elsewhere. Participants at these workshops agreed that the 20 questions were of high importance to the E. Asian and Australasian regions. They also highlighted the fact that these regions had unique characteristics (e.g. in terms of
biodiversity) that should be considered when addressing the questions. Participants felt that important issues, such as better risk communication, consideration of cultural differences and the impacts of natural medicines had also been overlooked.

Conclusions

The current study is the first to use the ‘key question’ approach to identify key issues around the exposure, effects and risks of PPCPs in the environment. We see this exercise as the start of a broader programme of work and in the short term we are planning a broader global survey to identify which questions are of most relevance to different stakeholders and why (additional questions proposed by the ‘local’ workshops will be included in this exercise). Alongside this survey, additional workshops are planned on select topics (e.g. antibiotic resistance) and the conclusions of the exercise will be disseminated to policy makers around the globe. We are optimistic that the results of this exercise will be invaluable in informing the design, coordination and implementation of future research programmes on PPCPs in the environment so that we may begin to fully understand the potential and relative risks of these substances in the natural environment and effectively control or manage these risks where necessary.
References


Table 1. Ranking of key questions by workshop participants. Potential approaches to address the questions are highlighted along with the inter-relationships of the questions and the degree of challenge required to address a question.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Question</th>
<th>Percentage of instances where question selected as most important*</th>
<th>Potential approaches to address the question</th>
<th>Related questions (numbered according to their rank)</th>
<th>Level of challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>How important are PPCPs relative to other chemicals and non-chemical stressors in terms of biological impacts in the natural environment?</td>
<td>48.5</td>
<td>Comparative assessment of risks posed by PPCPs compared to other stressors; Effects driven analysis on ecologically important endpoints for effluent samples to identify the relative toxicity of the chemical components; Eco-epidemiological studies.</td>
<td>will inform whether resource should be expended on many other questions, particularly those around risk management (e.g., 14); Data from 2, 3, 6, 17 may help to answer the question.</td>
<td>M-H</td>
</tr>
<tr>
<td>2</td>
<td>What approaches should be used to prioritize PPCPs for research on environmental and human health exposure and effects?</td>
<td>35.8</td>
<td>Review of existing prioritisation approaches to identify advantages and limitations and geographical representativeness; Development and application of new approaches for different scenarios and regions; Review of existing prioritisation approaches to determine whether similar PPCPs are highlighted against different prioritisation metrics.</td>
<td>5, 6, 9 and 19 may provide useful data.</td>
<td>L-M</td>
</tr>
<tr>
<td>3</td>
<td>Does environmental exposure to PPCP residues result in the selection of antimicrobial resistant micro-organisms and is this important in terms of human health outcomes?</td>
<td>34.3</td>
<td>Large-scale multidisciplinary studies to characterise the impacts of antibiotic residues on resistance in treatment systems, surface waters and soils; Characterisation of the degree of human exposure to resistance genes arising from the natural environment; Comparison of antibiotics in the environment with other pressures such as selection in the clinical setting and selection by other contaminants.</td>
<td>Could help inform 11.</td>
<td>H</td>
</tr>
<tr>
<td>4</td>
<td>How can ecotoxicological responses, such as histological and molecular-level responses, observed for PPCPs, be translated to traditional ecologically important endpoints such as survival, growth and reproduction of a species?</td>
<td>32.7</td>
<td>Generation of data on effects of a range of PPCPs on organisms at different levels (biomarker through to populations); Use of organism and population models to attempt to explain the linkages.</td>
<td>2 could inform which substances to focus on. Information from 6 may help to answer this question.</td>
<td>H</td>
</tr>
<tr>
<td>5</td>
<td>How can pharmaceutical preclinical and clinical information be used to assess the potential for adverse environmental impacts of pharmaceuticals?</td>
<td>32.4</td>
<td>Development of comparative datasets on preclinical, clinical and ecotoxicological data for a range of substances with different modes of action and physico-chemical properties; Evaluation of datasets to pull out major relationships</td>
<td>Information from 6 may explain different responses of humans and ecosystems.</td>
<td>M</td>
</tr>
<tr>
<td>6</td>
<td>What can be learned about the evolutionary conservation of PPCP targets across species and life stages in the context of potential adverse outcomes and effects?</td>
<td>31.1</td>
<td>Increased knowledge about the conservation of drug targets across environmental phyla and taxa through increased genome coverage; Application of adverse outcome pathway approach to understand relationships between target interactions and adverse effects on ecosystems</td>
<td>4</td>
<td>H</td>
</tr>
<tr>
<td>7</td>
<td>How can effects from long-term exposure to low concentrations of PPCP mixtures on non-target organisms be assessed?</td>
<td>30.1</td>
<td>Large-scale eco-epidemiological studies; Development of effective ecopharmacovigilance schemes; Long-term well controlled effects studies</td>
<td>5</td>
<td>H</td>
</tr>
<tr>
<td>Rank</td>
<td>Question</td>
<td>Percentage of instances where question selected as most important*</td>
<td>Potential approaches to address the question</td>
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<tr>
<td>8</td>
<td>How can ecotoxicity test methods, which reflect the different modes of actions of active PPCPs, be developed and implemented in customized risk assessment strategies?</td>
<td>29.8</td>
<td>Development of strategies, integrating information on pharmacology, target conservation and adverse outcome pathways, to identify best strategy for assessing the ecotoxicological effects of PPCPs</td>
<td>Could be informed by 4, 5 and 6.</td>
<td>L if other questions addressed</td>
</tr>
<tr>
<td>9</td>
<td>What are the environmental exposure pathways for organisms (including humans) to PPCPs in the environment and are any of these missed in current risk assessment approaches?</td>
<td>25.7</td>
<td>Review of potential pathways of release of PPCPs to the environment at different stages of the product lifecycle for different regions of the world; Analysis of existing risk assessment frameworks against this information; Refinement of frameworks to include ignored exposure pathways where appropriate.</td>
<td>Could help to inform 2 and 17.</td>
<td>L-M</td>
</tr>
<tr>
<td>10</td>
<td>How can the efficacy of risk management approaches be assessed?</td>
<td>23.8</td>
<td>Development of monitoring strategies (around use, disposal, occurrence and impacts) at different stages of the product life cycle. This should have some socioeconomic and cost-benefit analysis aspects included.</td>
<td>None</td>
<td>M</td>
</tr>
<tr>
<td>11</td>
<td>How can the risks to human health, arising from antibiotic resistance selection by PPCPs in the natural environment, be assessed?</td>
<td>23.6</td>
<td>Development of risk assessment strategies; Development of effective ecopharmacovigilance for antibiotics to assess the development and frequency of antibiotic resistance in natural microbial communities and clinical isolates.</td>
<td>Information from 3 could be helpful in the development of risk assessment schemes.</td>
<td>H</td>
</tr>
<tr>
<td>12</td>
<td>How can the uptake of ionizable PPCPs into aquatic and terrestrial organisms and through food chains be predicted?</td>
<td>22.4</td>
<td>Studies into the uptake, depuration and metabolism of a range of ionisable PPCPs with different properties into water, soil and sediment-dwelling organisms with different traits; Food chain studies with selected substance; Development of uptake models</td>
<td>May help with informing 1 and 15.</td>
<td>L-M</td>
</tr>
<tr>
<td>13</td>
<td>How can data on the occurrence of PPCPs in the environment and on quality of ecosystems exposed to PPCPs be used to determine whether current regulatory risk assessment schemes are effective?</td>
<td>22.1</td>
<td>Collation of data on the occurrence of PPCPs in receiving systems and on associated ecology; Analysis of data against exposure predictions from environmental risk assessments; Evaluation of quality of ecosystems receiving PPCPs; In the event that impacts cannot be ruled out, it will be necessary to tease out the impacts of PPCPs on a system against impacts of other stressors.</td>
<td>None</td>
<td>M-H</td>
</tr>
<tr>
<td>14</td>
<td>If a PPCP has an adverse environmental risk profile what can be done to manage and mitigate the risks?</td>
<td>19.0</td>
<td>Review of different management and mitigation options for different stages of the product life cycle; Generation of data on the efficacy of a particular option; Assessment of economic and other implications of an option so that benefits of a system can be weighed up against the potential costs.</td>
<td>Could be informed by data coming from 1, 3 and 10.</td>
<td>M</td>
</tr>
</tbody>
</table>
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Question</th>
<th>Percentage of instances where question selected as most important*</th>
<th>Potential approaches to address the question</th>
<th>Related questions (numbered according to their rank)</th>
<th>Level of challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Do PPCPs pose a risk to wildlife such as mammals, birds, reptiles and amphibians?</td>
<td>17.1</td>
<td>Development of exposure models for birds, amphibians and mammals; Evaluation of toxic effects of PPCPs on birds, mammals and amphibians using either existing preclinical data or well designed studies; Use of environmental monitoring studies.</td>
<td>Data from 5, 9 and 12 may provide useful information.</td>
<td>M-H</td>
</tr>
<tr>
<td>16</td>
<td>How can the environmental risks of metabolites and environmental transformation products of PPCPs be measured or predicted?</td>
<td>17.1</td>
<td>Development of improved analytical approaches for identifying metabolites and transformation products; Studies to assess relative effects of transformation products compared to parent compounds; Development of assessment schemes for transformation products.</td>
<td>Knowledge from 5 may help.</td>
<td>L-M</td>
</tr>
<tr>
<td>17</td>
<td>How can regions where PPCPs pose the greatest risk to environmental and human health, either now or in the future, be identified?</td>
<td>16.2</td>
<td>Evaluation of usage patterns of PPCPs in different geographical regions as well as local practices (e.g. for disposal and treatment of contaminated material) and potential differences in sensitivity of organisms both for now and in the future; Development of new exposure assessment models if appropriate; Use of information to establish potential risks.</td>
<td>Data from 9 will be useful.</td>
<td>L-M</td>
</tr>
<tr>
<td>18</td>
<td>What effluent treatment methods are effective in reducing the effects of PPCPs in the environment while at the same time not increasing the toxicity of whole effluents?</td>
<td>16.2</td>
<td>Targeted laboratory and field studies, that consider local conditions and constraints, to determine how PPCPs are removed in treatment processes and whether transformation products are formed; Use of biological based assessments to assess effectiveness of a particular treatment method.</td>
<td>Information from 4 and 8 could assist in the selection of biological endpoints to use; Data from 16 may help.</td>
<td>M</td>
</tr>
<tr>
<td>19</td>
<td>Can non-animal testing methods be developed that will provide equivalent or better hazard data compared to current in vivo methods?</td>
<td>13.2</td>
<td>Review of current non-animal methods; Assessment of information from selected methods against data from current in vivo methods; Development of recommendations on which non-animal methods can provide useful data.</td>
<td>Knowledge from 5 may help.</td>
<td>M</td>
</tr>
<tr>
<td>20</td>
<td>What is the bioavailability of non-extractable residues of PPCPs?</td>
<td>9.4</td>
<td>Improved analytical characterisation of the form of PPCP NERs; Controlled studies on the bioavailability of NERs of a range of PPCPs to soil and sediment-dwelling organisms with different traits over time; Manipulation studies to assess the impacts of e.g. climate change on the availability of NERs; Development of guidelines for NER assessment in risk assessment.</td>
<td>None</td>
<td>L</td>
</tr>
</tbody>
</table>

* - workshop attendees were sequentially presented with sets of 4 questions and asked to select the highest and lowest range question from the group. Using this process, all the 20 questions were then ranked. The number corresponds to the proportion of instances that a question was ranked highest in the sets of four questions by the attendees.

H = High - likely to require large, complex, multidisciplinary research programmes and development of new paradigms; M = medium – likely to require large, multidisciplinary programmes but many of tools required exist.; L – readily addressable through focused research programmes.
Figure legends

Figure 1. Major pathways of release of PPCPs into the environment. Reproduced, with permission, from Boxall (2004), EMBO Reports.

Figure 2. Relationship between results of acute and chronic studies, recommended for use in current regulatory assessment approaches, for PPCPs to fish and reported non-standard endpoints. Standard acute and chronic data (e.g. fish and invertebrate mortality, reproduction and growth) obtained from www.fass.se and a number of literature sources; non-standard endpoint data obtained from Corcoran et al., 2010.
Supplemental Material
Pharmaceuticals and Personal Care Products in the Environment: What are the Big Questions?


Contents

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2. Full question list submitted to the exercise................................................................................. 3
3. Questions taken forward to the workshop (broken down by breakout group)......................... 24
4. References ............................................................................................................................. 30
1. General Approach

Our study followed the question solicitation and prioritization methodology outlined by Sutherland et al. (2011). Initially, invitations to submit candidate research questions to a dedicated question solicitation website were widely distributed. Individuals were told that an ideal question should easily be translated into a directly testable research hypothesis. The answers to the question should be relevant to decision-makers, in so far as they would increase the effectiveness of business and policy decisions about the development or management of PPCPs and their interactions with the environment. Six criteria were suggested for candidate questions, they should: 1) address important gaps in knowledge; 2) be answerable through a realistic research design; 3) have a factual answer that does not depend on value judgments; 4) cover a spatial and temporal scale that realistically could be addressed by a research team; 5) not be answerable simply by “it all depends” or a simple “yes” or “no”; and, 6) if related to impact and interventions, they should contain a subject, an intervention, and a measurable outcome.

A total of 403 candidate questions were received in 161 submissions from individuals working for private sector manufacturers (17), private sector consultants (13), government scientists (42), government regulators or policy makers (19), academics (61), non-governmental organization representatives (3), and individuals from other organizations (6). Geographically, 3 submissions were from Africa, 9 from Asia, 25 from Australia and New Zealand, 48 from 15 European countries, 1 from Latin America, and 75 from North America. Removal of questions that did not meet the aspirational criteria, which were outside the scope of the exercise, or which were replicated, left 101 questions.

The 101 questions were then discussed at a two-day workshop involving experts from a range of disciplines (including ecology, environmental chemistry, ecotoxicology, pharmacology and chemical risk assessment) with an interest in the risks of PPCPs in the environment. Participants represented government (11), business (13), and academia (17), with representation from individuals based in North America (20), Latin America (1), Europe (6), and Asia (1), and from companies or industry associations with global operations (13). Four of the 41 individuals did not have PPCP subject specialist knowledge but had participated in previous key question exercises and acted as recorders and facilitators for this workshop. Participants selected the top 20 questions using the process employed at North American top 40 exercises for biodiversity science research questions (Fleishman et al. 2011; Rudd et al. 2011). The workshop comprised plenary and breakout sessions. Candidate questions were grouped in loose themes, and individuals were assigned to breakout groups based on their technical specializations.

Each breakout group was assigned 8-15 candidate questions and tasked with culling the set to two top 20 recommendations and one alternate. In prioritising the questions, groups were asked to consider the aspirational criteria described above. At this stage, an additional aspirational criterion was introduced: i.e. questions should be addressable by a research project or programme within a finite budget and timeframe (e.g. $10 million over five years). Participants in breakout groups sometimes combined candidate questions and developed alternate questions that captured key ideas from candidate questions. The 26 questions that resulted from the first day were discussed during a facilitated plenary session on the second day, during which the top 20 were selected. A web-based survey of the participants was performed following the workshop in order to rank the 20 questions in terms of importance. Potential approaches to address the questions were also identified.
2. **Full question list submitted to the exercise**

1. Are cladoceran reproduction assays appropriate for characterizing chronic toxicity of all PPCPs?

2. Are herbivorous, omnivorous and piscivorous birds at risk from PPCP exposures?

3. Are PCPs and pharmaceuticals present at concentrations in various environmental compartments that can cause significant adverse effects on biota (i.e., what is the risk and how do they interact with other contaminants)?

4. Are plants or earthworms able to take up the pharmaceutical and personal care products in the terrestrial environments?

5. Are proposed approaches to leverage mammalian or target organism pharmacology and toxicology data to predict aquatic and terrestrial wildlife effects of PPCPs encouraging?

6. Are side effects of medicines appropriately assessed using current regulatory testing regimes?

7. Are the levels sufficient to cause an effect in aquatic or terrestrial environments? What are the implications of the mixtures of pharmaceutical and personal care products in the environment?

8. Are the presence of pharmacological targets and their functions understood in aquatic plants, algae, invertebrates and vertebrates?

9. Are veterinary antibiotics and pharmaceuticals present in animal manure persistent and bioavailable in the terrestrial environment and do they have the potential to move off-site?

10. Can guidance be given on how to assess the environmental risks associated with chemicals referred to as pseudo-persistent?

11. Can we use our special knowledge about the mechanisms of action of pharmaceuticals in mammals to understand any possible interactive effects of mixtures in fish?

12. Clarification with respect to the differences between chemicals used in personal care products and active ingredients used in pharmaceuticals, and implications regarding how an ERA is performed for the respective class of chemical compounds.

13. Compare the relative environmental profiles of Pharmaceutical and Personal Care products

14. Do ADME characteristics in mammals predict ADME of pharmaceuticals in fish models? For example, are Vd, Cmax, t1/2, Cl values from humans predictive of those parameters in a 700 g fish or a red-eared slider turtle?

15. Do low levels of active ingredients present any harm to the Biota?

16. Do pharmaceutical and personal care products persist in the biosolids, majority of which is disposed on land in Australia? What is the fate of biosolid bounds pharmaceutical and personal care products?

17. Do PPCP in the environment affect reproduction or development in exposed wildlife?

18. Do the low-level mixtures of pharmaceuticals present in surface waters and sediments pose a risk to aquatic species

19. Does environmental exposure to antimicrobial residues, or to antimicrobial-resistance determinants selected for anthropogenically, promote resistance in environmental microorganisms, and create a reservoir that is then important in resistance development in human pathogens or commensals?
Does more need to be done to educate the public with respect to the disposal of un-used medicines?

Does resistance pass from the natural environment to the clinical environment and result in hospital acquired infections?

Effects of statins in the aquatic environment, are there any chronic effects to non-target organisms? What are the mechanisms of toxicity? Differences in species sensitivity?

How can sewage treatment be improved to remove pharmaceutical loads into the environment?

How can drugs be designed so that they have shorter half-lives in the environment?

How can risk-benefit modelling be used as a tool to direct research and policy decisions.

How can the BCF and BAF of ionisable organics be measured or modelled?

How can the man on the street help to reduce pharmaceutical impacts on the environment?

How can the universe of "unknown unknowns" be best reduced?

How can we effectively target which areas or regions are most at risk to health issues related to pharmaceuticals in the environment? Are these risks related to manufacturing, use, population demographics or the presence or absence of infrastructure?

How can we make sure, that PPCPs do not enter the environment in concentrations that are able to cause adverse effects on the ecosystems?

How can we reduce emission of pharmaceutical waste in developing countries?

How can we validate the assumptions made in environmental risk assessment for the partitioning, uptake and metabolism of pharmaceuticals where Kow assumptions are not valid?

How could you test the effects of long-term low level exposure of humans to pharmaceuticals in the environment?

How do risks from trace levels of pharmaceutical and personal care products in the environment compare to other human and environmental risks facing society, and how can we quantify these risks for comparison.

How important is the contribution of pharmaceuticals compared to other contaminants to real-world mixture toxicity?

How should we manage the risks associated with pharmaceuticals that have environmental data gaps?

How will environmental change affect the use and fate of pharmaceuticals and personal care products and how will this affect environmental risks compared to today?

If a drug has an adverse PBT and/or environmental risk profile what can be done to manage and mitigate the risks? Case studies?

If human health is at risk, how can we integrate human safety assessment and environmental risk assessment?

If the proposed approaches to leverage mammalian or target organism pharmacology and toxicology data to predict aquatic and terrestrial wildlife effects of PPCPs are promising, what data are needed to experimentally validate these potentially predictive models?
Improved methods and designing experiments to investigate ecotoxicological and risk assessment studies based on mixtures of organic contaminants is required. Can future research put more emphasis on this?

Is green drug design feasible? How will it work? And, what are the success criteria or protection goals? What if greener drug design is not feasible?

Is it appropriate to use Kow for ionisable organics, or would Dow be more appropriate as a trigger value within a regulatory context?

Is it possible to define the most sensitive species for testing of chemicals with specific modes of action?

Is the terrestrial compartment sufficiently protected by current ERA procedures?

Is there really a risk to human health through indirect exposure to pharmaceuticals?

Jurisdiction: How is it ensured that unused pharmaceuticals do not end up in the normal household waste? If they end up there what percentage will end up there?

Possibility of synergistic interaction of toxicity in mixture with contaminants other than pharmaceuticals.

Potential synergistic interaction in toxicity in mixture with other compounds including pharmaceuticals and chemicals other than pharmaceuticals.

Should medicines with both human and veterinary applications be assessed within a single framework to capture the ‘collective’ risk?

Should regulatory assessments account for the influences of site specific pH on bioavailability and effects of weak acid and weak base PPCPs?

Should regulatory assessments of PPCPs account for differences in metabolism and effects of enantiomers? E.g., Why is chirality not accounted for in PPCP ERAs?

Should toxicity equivalency approaches / mixture models be developed to prospectively assess the effects of PPCPs with common MOAs that will co-occur in effluent discharges? E.g., would a "risk cup" approach be appropriate?

Should we collect the same amount of human health and environmental data on personal care products, and especially "natural" products, as we do for pharmaceuticals?

Should Whole Effluent Toxicity test methods be expanded to include fish reproduction, biomarkers, or alternative endpoints such as behaviour?

To what extent the sewage treatment plants are effective in removing these compounds. Is the treatment process leading to real solutions or shifting the problem from aquatic to terrestrial environment?

To what extent will the emission of antibiotics to the environment, by drug use or production, provoke the development of resistance?

What are appropriate risk assessment processes for whole effluent and mixtures? Should the chemical-by-chemical assessment approach be abandon or does it still have an appropriate place in an assessment paradigm?

What are endocrine disruption potential of pharmaceuticals and its consequences in reproduction after long term exposure

What are safe levels for endocrine disruptors in the environment?

What are the "hot spots" for studying retrospective PPCP effects to aquatic and terrestrial wildlife in developed and developing countries?
What are the interactions between ionisable PPCPs and counter ions within a waste water treatment system, and how might this interaction influence fate and exposure?

What are the key environmental exposure pathways for organisms (including humans) to PPCPs in the environment and are we missing any of these in current risk assessment approaches?

What can be done to harmonize evaluation of risk to aquatic or terrestrial organisms from exposure to pharmaceutical residues?

What contribution do antimicrobials in the environment make to the selection of resistant viruses, bacteria and fungi?

What factors affect the bioaccumulation and bioconcentration of pharmaceuticals in aquatic and terrestrial systems and food chains?

What impact do they have on aquatic ecosystems, especially fish?

What is the bioavailability of pharmaceuticals that are tightly bound to soil and sediment particles and can changes in environmental conditions affect this?

What is the current understanding of whether major drug contraindications will correspond to mixture toxicity in aquatic and terrestrial ecosystems?

What is the effect of sludge and manure-associated PPCPs on soil ecosystems?

What is the effort done to evaluate the level of pharmaceuticals and personal care product in indoor environment?

What is the fate of pharmaceuticals and what is the sensitivity of ecosystems and its components?

What is the level of exposure of organisms to pharmaceutical and personal care products in the Australian environment? Are these compounds accumulating in the environment?

What is the relative hazard and risk of pharmaceuticals compared to other chemicals?

What is the therapeutic dose of a drug to a 30 g fish, or a threatened or endangered unionid mussel?

What makes pharmaceuticals different to other chemicals?

What needs to be done to extend current environmental risk assessment schemes for Europe and N. America to other geographical regions with different emission scenarios and cultural practices?

What use can we have of genomic tools for the work in pharmaceutical impacts on the environment?

What will be the future environmental exposure to nano-pharmaceuticals and what will be the implications for this in terms of environmental risk?

What would an environmental versus socio-economic benefit analysis look like for a human medicine? Agreed case studies (hypothetic or real)?

What would be the impact(s) to the ecosystem health (as well as to individual organisms) from exposure to very low levels of contaminants on ongoing bases)?

What would be the socio-economic consequences of restricting pharmaceutical use based solely on categorization schemes highlighting adverse environmental hazard or risk?

When is the total residue approach insufficient for ERA?
Why can't there be an organized research effort to use pharmaceuticals and veterinary products as molecular probes to look for homologous responses in other species to expand our basic understanding of how organisms respond to well understood chemicals?

Why doesn't SETAC and other organizations outwardly support SMARxT Disposal and other trademark efforts to reduce PPCPs in the environment?

How can we assess risk of organic extract oil as a cosmetic and pesticide component?

Are antibiotic residues in the environment, especially from agriculture and aquaculture, contributing to the development of resistance in wildlife, and is there evidence that this could affect human health?

Drugs will not equally provoke biological effects on a per kg basis; can the DDD (as established by the WHO) serve as a proxy for the probability of inducing an effect? We could test the null hypothesis with algae and daphnia using fixed concentrations of a suite of drugs with different DDD values.

Environmental regulations for drugs are based on a threshold of effect. There is a need for an independent and non-industry sponsored review of the supporting data and review this approach in light of "non-threshold" concerns like carcinogenicity, endocrine effects, and antimicrobial resistance.

How are drugs from agricultural use actually entering the environment; that is, what proportion is direct liquid run-off to surface or ground water rather than "leachate from manure" applied to agricultural land?

How do terrestrial and aquatic ecosystem changes directly or indirectly affect human health? What are the aggregate effects on ecosystems of current-use and emerging toxicants? What are reliable scientific metrics for detecting chronic, long-term changes in ecosystems?

Do we need to be concerned about drug routes of exposure other than dietary for non-target terrestrial animals?

Effects data for non-target species are lacking for many drug classes, so priorities are needed for testing. Prioritization cannot be based on exposure or persistence alone due to potency of some drugs. How then should testing be prioritized?

How can pesticide registration ecotoxicity data (e.g. from the US) be better leveraged/used for assessing risks of pesticides registered as veterinary drugs?

Some have suggested use of drug development data for target species (e.g. humans) to identify potentially sensitive species/endpoints in terms of eco effects, based on degree of structural conservation of molecular drug targets. Is this reasonable? How could one demonstrate a "proof of concept"?

What would an efficient approach be for "discovery" of potential impacts of drugs, not related to their therapeutic targets, on plants, invertebrates and vertebrates without testing everything?

How to derive water quality guidelines or trigger values for PPCPs?

What are the realistic approaches and methods for Ecological Risk Assessment of mixtures of PPCPS in the receiving environment?

How can we measure mixture toxicity of PPCPs in the aquatic environment?

Are regulators giving as much emphasis on the potential for endocrine activity to pharmaceuticals and personal care products as they are to agrochemicals?
What are the "safe" levels for discharge of PPCPs to the environment and in drinking water? This is currently based mostly around detection limits but is this representative or can we manage with higher levels?

What are the impacts of continuous release of complex PPCP mixtures, which are largely below instrument detection limits, to the environment?

What are the sub-lethal effects of PPCPs and how important is this for management? e.g., spread/development of antibiotic resistance, modification of gender dominance?

What is the risk of bioaccumulation and impacts of PPCPs, particularly in human target species?

What sublethal effects can be observed for aquatic populations and at ecosystem level after chronic exposure at low concentrations?

What physical-chemical characteristics distinguish PPCPs from other chemicals that results in greater or lesser concern compared to "general chemicals"?

Would the regulation of PPCPs benefit from more clear or adjusted jurisdictional boundaries regarding their approval and use in commerce relative to environmental safety?

How can we prioritize which pharmaceuticals pose a threat to the environment? What are the effects and risks we anticipate?

How large is the impact of antibiotic production and usage on resistance in environmental bacteria? On human pathogens?

How will chronic exposure to mixtures of APIs affect organisms? Will there be epigenetic effects? Will effects be multigenerational?

Risks to the environment will always need to be weighed against benefits for human health, but should we be aiming to replace certain compounds with other, less environmentally dangerous APIs?

Given that environmental exposure is most likely to be continuous and chronic what are the appropriate endpoints to be explored in aquatic vertebrates / invertebrates?

How appropriate is chemical analysis for measuring the presence of pharmaceuticals in the environment? Would biological monitoring be more appropriate?

Is it possible to get industry to share the wealth of data they have gathered over the years on the various pharmaceuticals that are likely to cause environmental concern? Are any moves being made in this direction?

How widespread is the problem with emissions from pharmaceutical production?

Is a decreased selection pressure for acquiring antibiotic resistance, i.e., lower emissions of antibiotic substances into the environment, likely to result in also a lower abundance of antibiotic resistance genes in environmental bacteria? (Or is the acquired resistance genes preserved?)

What are the major drivers for antibiotic co-resistance?

What are the long-term effects of chronic exposure to low levels of PPCPs released into the environment on aquatic organisms including amphibians?

How much of a PPCP in surface water is bad for the environment?

What occurs in the environment in an aquatic organism (i.e., fish) when exposed to mixtures of pharmaceuticals with regard to drug-drug interactions?
Can the effects of PPCPs be isolated in sublethal toxicity tests conducted on (marine) organisms using whole municipal wastewater effluent?

How can a waste discharge manager more effectively assess the potential for effects of the PPCPs he/she monitors, particularly considering we are discharging an effluent that contains many other chemicals as well?

What is the effectiveness of various different treatment technologies on the removal/destruction of PPCPs in municipal wastewaters, sludges and biosolids?

What is the relevance of the effects of PPCPs in biosolids applied to land, particularly in relation to the effects of all the other chemicals potentially found in biosolids?

What is the relevance of the effects of PPCPs in relation to the effects of other chemicals that any given organism is exposed to?

What is the status of analytical methodologies for PPCPs and what are the implications of comparing results from non-standardized methods?

How can quantum chemical methods and atomistic simulations play a role in understanding environmental toxicology on the molecular scale?

In which chemical forms do PPCPs exist in aqueous environments: metabolic by-products, environmental degradation products, or original formulations? How does pH affect their chemical structure?

What is the PPCP disposal effect on marine ecosystems?

What steps can be taken to ensure protection of fish and their habitat from release of endocrine disrupting chemicals and other toxicants into the environment prior to our fully understanding potential adverse consequences of such releases?

What is the half-life of pharmaceutical products with high efficacy in the environment?

What are the main criteria test guidelines should met to address the risk for aquatic and terrestrial organisms? Are the current valid OECD guidelines (mentioned in the guidance document) appropriate to address the risk from pharmaceuticals with special mode of actions?

Can a laboratory test be devised to measure (or help to predict) pharmaceutical degradation half life to a reasonable degree of accuracy?

Can genomic techniques be used to identify modes of action that would be significant in the aquatic environment?

Can so-called "bound residues" of pharmaceuticals be removed from sediments and/or sludges by any process that might realistically occur in the environment?

Is it demonstrable from first principles that human metabolites of pharmaceuticals will have a lower ecotoxicity than the parent compound?

What is the occurrence (based on adequately sampled concentrations) of PPCPs in the environment?

What is the effect of pharmaceuticals and mixtures of pharmaceuticals on the microbial community and the ability to deliver vital ecosystem services?

What about long term uptake of pharmaceuticals by crops irrigated by wastewater treated by activated sludge, sand filtration and chlorination in which such compounds exist? What the dangers are expected to be for human health and animals (example: clover, animals, milk, humans).
Which chemicals have the potential to cause adverse biological effects?

How do the quantifiable adverse ecological and biological effects of pharmaceuticals and personal care products compare with the known effects of other natural and synthetic contaminants in the environment?

How can we determine the regulatory-level risk of these compounds in an efficient, timely manner?

What methods can be used for removal of cyanobacterial toxins?

What quantities of unused pharmaceuticals with unknown potential impacts on the environment are potentially in the community?

What are the effects to aquatic and terrestrial organisms from the chronic exposure to complex mixtures of PPCP?

Given that most PPCPs are discharged primarily via the use and disposal of domestic use, have there been suitable site-selection criteria been developed to ascertain the true potency of these materials in receiving water communities?

The concentration of various PPCPs has required an understanding of MoA’s, especially in low concentrations. Have these chemicals been truly assessed for MoA that is relevant to receiving water communities?

Is the contribution of physiologist/biochemists on subtle/specific/low concentrations effects of pharmaceuticals on environmental fauna considered of some importance for guidelines definition, risk assessment, etc...?

Pharmaceuticals are specifically designed to induce specific effects at very low concentrations. How these subtle / low-dose / highly specific effects by single environmental pharmaceutical or their mixtures can be taken into account for guidelines development?

Increased information about the degradation patterns of these substances, the occurrence, persistence and ecotoxicity of degradation products as well as analytical techniques to detect them.

Many PPCPs are polar and ionizable substances to which the common models for partitioning and adsorption are not applicable. Part. and ads. are strongly related to bioavailability, and a qualitative as well as quantitative description of these mechanisms would greatly increase understanding.

Further research on mixtures. What are the potential mixture effects, what is the impact of mode or mechanism of action of individual compounds on any mixture effect, what are the dose response kinetics for mixture effects?

The presence of PhACs in the environment in high ng/L concentrations is pretty clear. What is unclear is what a safe concentration is? Access to pharmaceutical company’s tox data would greatly improve our understanding of that.

What cost-effective technologies and other risk management strategies are best to reduce environmental releases of PPCPs from a variety of sources (e.g., from wastewater treatment plants, drinking water plants, concentrated animal feeding operations) that are adversely affecting ecosystems?

How to test for the effects of long-term low level exposure of humans to pharmaceuticals in the environment?

What are the major pathways of exposure of the major pharmaceuticals found in municipal effluent to the aquatic fauna and flora
What is the long-term toxicity of low concentrations of pharmacological mixtures to aquatic life?

Which trophic levels are at risk to a given class of pharmaceuticals?

What are the spatio-temporal cycles in ecosystem response to constant exposure of PPCPs with respect to its ecosystem services and how can they be actively managed to sustain an environment capable of enduring these exposures.

Will a regulatory framework be created that considers not only toxicological endpoints but concentration target, environmental loadings and presence of the substance in potable water after pharmaceuticals are released from domestic waste water streams?

What are differences in the fate and effects of the enantiomers of chiral PPCPs?

Are threshold limits proposed in the new Municipal Wastewater regulations protective of the aquatic receiving environment?

Does advanced wastewater treatment remove priority trace contaminants of concern to levels below which effects in the receiving environment are not expected?

How do researchers separate effects from PPCPs and other key stressors in this system such as ammonia, and water temperature on aquatic biota?

How do reproductive impacts demonstrated in a fish population exposed to treated sewage affect higher levels of biological organization (fish community, ecosystem)?

What are the links between estrogens or anti-androgens and reproductive dysfunction in the fish collected downstream of treated sewage discharges?

What are the most environmentally friendly methods to address the issue of veterinary and human pharmaceuticals in biosolids?

What are the threshold levels PPCPs which elicit a response in aquatic biota?

What is the fate, persistence and distribution of PPCPs in land applied biosolids?

What is the relative contribution of hormones derived from livestock operations compared to human waste streams to the receiving environment?

What is the relative contribution of PPCPs to natural hormones from human sources to effects in the receiving environment?

What is the relative contribution of veterinary drugs to PPCPs from human sources in the receiving environment?

Impacts or effects in all environmental compartments (in terms of detected concentrations) and in all biota

Do observed concentrations of PPCPs translate into specific or aggregate effects of PPCPs on individual organisms, and does this in turn translate to effects on populations of aquatic organisms and/or ecosystems or ecosystem function and services.

Are there any health effects from trace levels of PPCPs in drinking water, acting either alone or in combination?

Are the actions of pharmaceuticals conserved across different groups of organism?

How are the actions of pharmaceuticals affected by other stressors in the environment?

How do different classes of pharmaceuticals affect target species?

How does the interaction of a pharmaceutical with its receptor translate to an individual or population level effect?
What are the trans-generational impacts of exposures to pharmaceuticals?

Appreciation of chronic AOPs in non target organisms and linkage between mammalian and aquatic species toxicity responses and predictability based hereon

At what environmentally relevant concentration are PPCPs causing adverse effects to aquatic organisms that can negatively affect populations and communities of these organisms?

How can the variability (both environmental and anthropogenic) in emissions and exposure be more readily quantified to achieve a more realistic representation of spatial and temporal environmental exposure for regulatory decision making?

How does one calculate exposure risk for pharmaceutical mixtures in drinking water and integrate this input with possible interaction(s) with other environmental contaminants.

Do PPCP behave in the environment (e.g., transport and fate, toxicity) as predicted by SARs based primarily on industrial chemicals?

Can antibiotic resistant bacteria found in the environment be a potential threat to the human health care?

To what extent does the personal care products affect human life cycle (in particular fertility)?

Can we make more out of the available data if data transparency is increased and the data is coordinated more effectively?

Does ERA and ecopharmacovigilance need to consider off-label used of drugs?

How can we predict which pharmaceuticals are most likely to pose a risk?

Is ecopharmacovigilance a useful concept? If so, what would this mean in practice?

What are the risks associated with long-term exposure to pharmaceuticals at low levels on ecosystems and human health based on current and projected environmental concentrations, and how can they be assessed?

What makes an ERA fit-for-purpose?

How do we develop an integrated approach to effects based prioritization of pharmaceuticals in the environment? How do we ensure that the approach is balanced and inclusive of all active pharmaceutical ingredients?

Pharmaceuticals are biologically active compounds with specific modes of action. How do we integrate MOA based evaluations of aquatic species into risk assessments and eventually into the regulatory framework?

How do these biologically active chemicals impact or alter the functioning of food webs, either soil, terrestrial, or aquatic?

Do environmental levels of antibiotics induce/select for/have an impact on the prevalence of antibiotic resistance genes?

How can we resolve the effects of low concentrations of pharmaceuticals from the effects of the multiple other co-contaminants that are commonly encountered in real-life exposure scenarios?

How do we measure (biological/ecological) impacts of pharmaceuticals & personal care products (gene - individual - population)

Classifications of PPCPs by expected mode of action to test interactions?
How do the many changes in molecular endpoints translate into population health?

Interaction between PPCPs?

Can we identify biomarkers that will link specific chemicals or chemical classes directly to population or community-level impacts in aquatic ecosystems?

Based on current knowledge, what are the effects/risks of highest concern (human and environmental) related to emissions of pharmaceuticals?

How can economical incentives be created for industries to reduce environmental emissions from manufacturing?

How can the recent fast development in next generation sequencing and related technologies best help research on PPCPs in the environment?

How can we assess the risks that a pharmaceutical entering the external environment promotes resistance mechanisms, of a type that would be clinically relevant, and that these mechanisms then spread to the human microflora and eventually pathogens?

How can we best take advantage of the vast information on pharmaceuticals (kinetics and dynamics) generated from studies on mammals, including man?

How should we best incorporate sublethal responses of drugs in organisms in laboratory tests into the greater picture of environmental risk assessment?

Since antibiotic resistance, once developed, tend to spread all over the world, should we put most focus on managing the worst environmental antibiotic pollution sources regardless of where they are located, or should each country focus on their own backyard?

What are the (probably rather few?) pharmaceuticals that indeed have adverse environmental effects as a result of (normally low-level) emissions from usage?

What are the direct emissions of active pharmaceutical ingredients from manufacturing sites world-wide (concentrations, volumes) and what are the risks (human health and ecological) associated with such releases?

What are the possibilities and limitations in predicting effects of pharmaceuticals on wildlife based on similarities and differences between (the genomes of) species?

What are the risks for antibiotic resistance to develop in human pathogens as a result of environmental emissions of antibiotics at levels higher than human therapeutic levels (as found in industrial effluents from for example India, China and Korea)

What effluent treatment methods are effective in reducing the APIs causing the highest environmental risks, at the same time 1) not increasing the toxicity of the whole effluents, 2) being economically feasible, and 3) also being able to remove other unwanted organic contaminants?

What factors are most important for determining the flow of antibiotic resistance genes from environmental bacteria to human pathogens?

How do we determine (and convince the public that there are) environmental concentrations of PPCPs that are NOT of concern to organisms in lakes & rivers?

How do we link biomarker "screens" (YES, YAR etc) of MWWE or individual PPCP effects to real effects in the environment?

Risk Assessment of PPCPs is done chemical by chemical (or at best - by chemical class with similar MOA). How do we relate this to the MIXTURE of PPCPs in municipal wastewater effluents and in the environment?
Which pharmaceuticals and personal care products should we worry about? Which ones cause effects in the environment?

What are the high-risk environments for transfer of antibiotic resistance genes to human pathogens?

What are the risks that the promotion of antibiotic resistance genes seen in highly antibiotic-polluted environments will spread to pathogenic bacteria, and how does this affect our ability to fight bacterial infections?

How do specific sublethal effects and biomarkers of P&PCPs translate to ecological effects?

Risk assessment & prioritisation of P&PCPs in aquatic and soil ecosystems - which are the highest priority chemicals and what are their risks to the environment?

What is the epidemiological evidence that any PPCP chemicals are linked to disease in humans or wildlife?

Is it reasonable to assume that human metabolites as well as aerobic environmental TPs will have a lower inherent toxicity than parent compound? Is it possible to establish a risk quotient (RQ) below which the above metabolites and TPs may be dismissed without further consideration?

Can you correlate the harmful effects of PPCPs to their structural characteristics?

For pharmaceuticals: How can information generated during the drug development process on subjects such as mode of action, ADME (adsorption, distribution, metabolism, excretion), efficacy, safety, etc. be applied in the evaluation of potential effects on ecological receptors?

What data or studies exist to show that simple acute toxicity tests provide sufficient information to assess potentially chronic exposures to PCCPs for the wide spectrum of PCCPs? What is the range of known Acute-to-Chronic Ratios (ACRs) and do these ACRs reflect different modes of action?

Is the climatic difference between north and south or between coastal and continental, humid and dry, e.g., for North America and Europe, significant for the environmental fate (and ecotoxicity) of PPCP? If so, do we need to integrate that difference in PEC or PNECs or not?

What are the necessary tests (ordered by importance for fate) and defaults for modelling the environmental fate in surface waters? How can partitioning, surface water biodegradation, photodegradation and advection be intelligently integrated, what compartmental defaults should be used for modelling?

Are concentrations of antibiotics in the environment potentially high enough to lead to increases in antibiotic resistance?

What are the fate and transport of these compounds in WWTPs?

How do mixtures of PPCP affect aquatic life?

Removal of PPCP from drinking water?

Removal of PPCP from wastewater?

Given the conservation of drug targets between humans and other species, how do we take into account the potential for non-traditional effects (e.g. behavioural) associated with exposure to pharmaceuticals designed to perturb those metrics?

What is the ecological relevance of environmentally relevant concentrations?
Do pharmaceuticals in the environment result in adverse effects and can we live with these effects?

What role do pharmaceutical metabolites play in the risk posed to the environment from PIE?

What is the impact of dissimilarly acting mixtures of pharmaceuticals in the environment?

Are CAFO's a significant part of the problem of release of PPCP's to aquatic environments, and if so, will they be required to treat effluent?

Are there multi-generational impacts of low, chronic doses of PPCP mixtures to aquatic and amphibious life?

How do impacts of PPCP's at the molecular and cellular level intersect or support observations at the environmental or community level?

How would phasing out the use of antibiotics in CAFO’s, except in obviously sick animals, change the impact of effluent on aquatic systems?

If waste-water treatment plants are required to implement PPCP degradation technologies, will all plants be required to install them? If not, what criteria will be used to determine which plants install them, and who will develop the criteria and make the decisions?

What interactions do specific or multiple PPCP’s have at the molecular level, particularly with respect to reproductive effects in aquatic life?

What is the potential economic impact of applying PPCP treatment technologies to large waste-water treatment plants, and what developing technologies could potentially decrease the economic impact?

How can we group pharmaceuticals and study them using representatives within an MOA to illustrate the effect of mixtures of pharmaceuticals within and across MOA on Aquatic and Terrestrial Organisms?

What are the various exposure profiles in freshwater and terrestrial ecosystems associated with sources of pharmaceuticals both human and animal?

What endpoints both traditional as well as molecular and behavioural can be used to identify MOA?

May alterations potentially resulting from climate changes modify substantially the toxicity, mechanisms of toxicity and pathways of biotransformation of these products?

What are the long-term effects of exposure to low concentrations of pharmaceuticals and personal care products, including complex mixtures, on populations of marine, especially estuaries?

What are the toxicological interactions between these substances and other environmental contaminants?

How widespread is the environmental pollution from pharmaceutical production and what is the local and global environmental impact?

To what extent will emission of antibiotics to the environment (through usage or production) provoke development of resistance that will have a significant impact on our health care? What is required for antibiotic resistance developed in the environment to spread to human pathogens?
What sewage treatment technologies are the most cost effective and best from an environmental perspective? How can we create economical incentive for the pharmaceutical industry to take care of the pollution from the production?

What is the relative contribution of the veterinary drugs and what of this is not for the treatment of animal safety issues? Are there alternatives for growth promotion?

What is (are) the effect(s) of multiple stressors in the receiving ecosystems?

What is the most suitable way to engage the communities in this issue?

What are the mechanistic effects of pharmaceutical mixtures?

What is the best prioritization strategy to determine how the research efforts should be directed to minimize the negative effects of PPCPs on human health and ecosystems?

Effects of estrogens have been documented in the field, whole lake additions and in laboratory studies. What are the cumulative effects of multiple MWWE discharges in a receiving environment and are reproductive effects masked by nutrient effects?

Intersex has been documented in a number of species. Do we know enough about the frequency of this condition in unexposed populations?

Is there really anything to worry about in municipal wastes other than nutrients?

Do mixtures of low concentration of PPPCs give more effect to aquatic organisms than addition of individual impact?

How to prioritize which of these compounds a POTW should monitor and regulate with respect to effects on the marine environment?

What are effective policies and/or changes to waste management which can be integrated into environmental risk assessment to reduce adverse impacts of pharmaceuticals and personal care products in the environment?

Can the levels of pharmaceuticals measured in the aquatic environment be linked to expected levels in aquatic organisms, i.e., what factors can be used to predict bioavailability in aquatic organisms?

Ecotoxicological responses of marine organisms to triclosan and methyl-triclosan?

Factors leading to the methylation of triclosan in the environment?

Occurrence of triclosan and methyl-triclosan in stormwater or industrial effluents?

How can water and waste water utilities be assured that they are removing Pharmaceuticals and Personal Care Products from the water which will be sold to our customers or discharged to streams? What types of treatment techniques or systems will break-down and remove these products?

Is fish intersex caused by pharmaceuticals?

How can we combine the need of pharmaceuticals to treat disease and the environmental protection?

Of those PPCPs which persist in the aquatic environment, which aquatic life act as robust sentinels of potential human health effects?

What would be the impact(s) to overall ecosystem health (as well as to individual organisms) from exposure to very low levels of contaminants on an ongoing basis?

Can ‘omics’ and other novel technologies be used to identify pharmaceuticals that might pose a risk to the environment? If so, how?
Do mobile genetic elements that encode resistance in the environment pass resistance on to clinically important species?

How can information on the toxicity (e.g. side effects) and pharmacology of a pharmaceutical in humans be used to provide information on potential ecotoxicological and ecological effects (and vice versa)?

How do non-standard effects endpoints that have been observed in organisms exposed to pharmaceuticals, such as biomarker responses, relate to ecologically important endpoints such as survival, growth and reproduction?

How important is metabolism for reducing bioconcentration in wildlife?

How important is the contribution of pharmaceuticals compared to other contaminants to real-world mixture toxicity?

How should pharmaceuticals be prioritised for assessment in terms of their impact on the environment?

To what extent do pharmaceuticals in the environment get into food supplies and what are the implications of this in terms of risks to human health?

What are the effects, if any, of bound residues of pharmaceuticals in soils and sediments on organisms?

What are the risks associated with long-term exposure to pharmaceuticals at low levels on ecosystems and human health based on current and projected environmental concentrations, and how can they be assessed?

What contribution do residues of antimicrobials in the environment make to the selection of resistant viruses, bacteria and fungi that are important for human and animal health?

What data which we currently collect are most valuable for risk assessment and what can be discarded?

What evidence is there that pharmaceuticals in the environment are affecting ecosystems and human health?

What factors affect the bioaccumulation and bioconcentration of pharmaceuticals in aquatic and terrestrial systems and food chains?

What is the level of risk of pharmaceuticals to wildlife (e.g. birds), ecosystem service provisioning and broader biodiversity?

What needs to be done to extend current environmental risk assessment schemes e.g. for Europe and N. America to other geographical regions?

What strategies exist to reduce environmental exposure and effects of pharmaceuticals when a potential risk is identified?

When do the standard risk assessment methodologies fail to identify the potential for adverse environmental effects?

Which catchments or regions are most at risk from exposure to pharmaceuticals?

How to create a general database for all the studies

How can we identify their adverse effects in complex mixtures like sewage effluents?

How similar are the occurrence patterns around the world (i.e. developed and developing countries)?
In contrast to ECD’s, PPCP’s are a heterogeneous group from the point of view of the biological effects they elicit. It is the common source enough as rationale justification to evaluate them all together?

There is any relationship among their clinical mechanism of action in humans and in wildlife?

There is any relationship among use and environmental occurrence patterns?

Which are the differences that distinguish PPCP’s from other traditional pollutants? Do we need to develop specific ecotoxicological methods of assessment?

Which are the environmental levels in relation with the sensitivity of local, especially considering highly biodiversity sites?

How might chemicals be grouped for evaluation?

How might chemicals be prioritized for environmental monitoring?

How might the adverse impact (risk) of one chemical exposure be measured against all other chemical exposures, and how might all chemical exposures be measured against all other stressors?

What is the effect of organism exposure to multiple PPCPs?

Are wastewater treatment plant discharges, to water and/or irrigating crops, the only plausible route for significant build-up of pharmaceuticals and personal care products in the environment?

Is there a need for more studies investigating long-term, low-level effects of PPCPs in aquatic and terrestrial systems in support of assessing potential risks?

Why is there not more emphasis on communicating the risks of PPCPs to the public?

Understanding of the relative potencies of metabolically or environmentally modified molecules and the environmental chemical factors that can lead to "reactivation" of conjugated molecules.

Ecological relevance of pharmaceuticals in the environment: What methods can be employed to determine/measure in situ effects of individual APIs or mixtures of similar acting compounds? How predictive are the laboratory data produced for risk assessments?

Mechanism based testing strategy: The ecotoxicological testing of APIs for risk assessment is based mainly on standard procedures. How can we develop specific test methods, which appreciate the different modes of actions of APIs, for example as it is done for endocrine active compounds?

What happens to spent fermentation media? Fermentations are used to create many drug products. After fermentation is complete the drug is removed from the fermentation mass. What happens to the spent fermentation mass? Is it re-used, used for animal feed or discarded to the environment?

What is the environmental impact of chemicals in suncare products to marine environments? Many tons of suncare products are used each year and enter the marine environment what is their fate and do they negatively impact fish, plankton or living corals?

Beyond biomarker induction, we need consensus on criteria for assessing the magnitude of environmental effects and a suite of standardized lab tests with endpoints directly related to the environmental criteria.

Are pharmaceutical residues present in the environment contributing to the current decline in biodiversity?
319 Can biomarker responses be related to ecologically relevant population endpoints?

320 Can concentration thresholds of concern be used to address mixture risks?

321 Can current or new technologies or approaches be used to identify the most sensitive species for testing based on mode-of-action of a given pharmaceutical?

322 Can drug-drug interactions be used to identify potentially synergistic effects in pharmaceutical residue mixtures?

323 Can more accurate partitioning models be developed for pharmaceuticals so that environmental concentration estimates are more accurate?

324 Can threshold concentrations based on biological activity be determined that are generally protective of humans and environmental organisms?

325 Can wild populations be systematically sampled to determine in vivo concentrations of prioritized pharmaceuticals?

326 Does the presence of anti-infective pharmaceutical residues in the environment contribute to the development of resistance?

327 How can pharmaceutical preclinical and clinical information (ADMET) be used to assess the potential for adverse environmental impacts and customize subsequent testing strategies?

328 Is the current standardized testing regime and environmental risk assessment methodology for pharmaceuticals protective of both humans and environmental organisms?

329 Is there an agreed prioritization approach to assess pharmaceuticals based on their intrinsic hazards and potential risks to the environment?

330 Is there any evidence of increased environmental exposures to humans or organisms via concentration or accumulation effects in the terrestrial systems and associated food chains?

331 What are the effects of bound residues of pharmaceuticals and aging processes in soils and sediments?

332 What are the gaps in current pharmaceutical and ecological knowledge that need to be filled in order to assess potential human and ecosystem effects of long-term low level exposures to pharmaceuticals?

333 What human sensitive sub-populations or regional or local ecosystems would be at the most risk from exposure to pharmaceutical residues?

334 Will rising concentrations of pharmaceutical residues as a result of decreased water use and changing precipitation patterns put these watershed ecosystems at more risk?

335 What is the environmental fate of these types of substances?

336 What is the ecotoxicology of long chain (> C8) and sulfonated perflourinated chemicals?

337 What level of pharmaceuticals and personal care products will not impair water quality for aquatic life and human health?

338 What is the impact of PPCP from STPs in tropical marine environments

339 To what extent can the intended mode of action of pharmaceuticals be used to predict likely impacts on ecosystems?

340 How do pharmaceuticals impact trophic levels and are there synergistic effects?

341 Since there is evidence that P&PC actives are getting into wastewater are there economical technologies that can be added to waste treatment facilities that can inactivate these actives?
Are any excipients of environmental relevance?

Are appropriate disposal systems for pharmaceuticals available?

Can hygiene management in stables and changes in animal husbandry reduce the amount of veterinary pharmaceuticals used? How can such good management practices be implemented bindingly?

Do antibiotics have indirect negative effects in the environment by selecting certain microbial strains?

Do emissions from production sites of pharmaceuticals pose a risk to the environment? Is additional regulation needed (in the EU, North America, in Asia)? If yes, what would be an appropriate regulation?

Do human and veterinary pharmaceuticals in the environment pose a risk to humans? Does the current risk for humans differ between regions?

Do the OECD guidelines currently used for the environmental risk assessment of human and veterinary pharmaceuticals cover the appropriate organisms? Would it be necessary to add molluscs to the testing program?

How can an environmental risk assessment be conducted for pharmaceutical active ingredients that are not standard small molecule drugs (e.g. biopharmaceuticals and nanomedicines)?

How can doctors, veterinarians, farmers, pharmacists, etc. be educated about the risk human and veterinary pharmaceuticals pose to the environment?

How can transformation products of active ingredients of human and veterinary pharmaceuticals be assessed?

How could all information on occurrence, fate, and effects of human and veterinary pharmaceuticals be summarized and made available to stakeholders and the interested public (maps with all concentrations of detected pharmaceuticals? ERA-wiki?)

How could duplicate testing of active ingredients of human and veterinary pharmaceuticals be avoided?

How could effects of pharmaceuticals in the environment be detected within the pharmacovigilance system?

How could measures to prevent and cure illnesses without the use of pharmaceuticals be promoted?

How could monitoring be used to evaluate the effectiveness of environmental risk assessments for human and veterinary pharmaceuticals?

How could non-lipid based mechanisms of accumulation of active ingredients into organisms be taken into account for the environmental risk assessment of human and veterinary pharmaceuticals?

How could the risk for the environment be taken into account in the benefit-risk-assessment for veterinary pharmaceuticals?

How do human and veterinary pharmaceuticals affect biodiversity and protected species? Are those effects covered by the current risk assessment?

How should a monitoring scheme for authorized pharmaceuticals which potentially pose a risk to the environment be designed?
How should environmental concentrations of human and veterinary pharmaceuticals be predicted (PEC calculation) in order not to underestimate the concentration in the environment (no PECs lower than MECs)?

How should genotoxicity of an active ingredient be assessed with regard to environmental organisms?

How should non-extractable residues of human and veterinary pharmaceuticals be assessed? How could climatic variability (seasonal as well as long-term) be taken into account in the assessment of NER?

How should PBT pharmaceuticals be managed?

Is a limit of 0.1 µg/l for human and veterinary pharmaceuticals in ground water protective for the ecosystem and humans?

Is it a realistic assumption that green pharmacy will reduce the risk human and veterinary pharmaceuticals pose to the environment in the coming years, e.g. will actives that easily mineralize be developed?

Is it acceptable that human and veterinary pharmaceuticals enter ground and drinking water?

Is it appropriate to trigger an experimental environmental risk assessment based on a threshold predicted environmental concentration? If yes, which trigger value would be appropriate?

Is there a correlation between dose and effect values in the environment? Do pharmaceuticals which are used at lower doses show effects at lower concentrations? If yes, which consequences does this have for the use of trigger values and the prediction of environmental concentrations?

Should any non-standard endpoints be included in the environmental risk assessment of pharmaceuticals?

Should climatic differences be taken into account in the environmental risk assessment of human and veterinary pharmaceuticals (within the EU and between regions)?

Should pharmaceuticals be classified and labelled (GHS)?

What are the benefits and risks of nano-pharmaceuticals for the environment?

What effects does the use of wild plants or animals as pharmaceuticals have on the environment/biodiversity? If there are adverse effects, would additional regulation be needed?

What is the correct disposal pathway for human and veterinary pharmaceuticals to avoid entry into the environment? Are there differences between regions?

What would be an appropriate approach to assess mixture toxicity in the ERA for human and veterinary pharmaceuticals?

What would be an appropriate test for inhibition of microbial activity in the environment (besides STPs) by pharmaceuticals?

What would be effective risk mitigation measures for human and veterinary pharmaceuticals?

What would be the best approach to take the use of an active substance in several products into account for exposure assessment for human and veterinary pharmaceuticals? How can the use of this active for other purposes (e.g. as pesticide) be taken into account?
What would be the best way to assess the environmental risk of existing human and veterinary pharmaceuticals?

Which additional environmental standards should be implemented for the production of human and veterinary pharmaceuticals?

Which effect does the price of pharmaceuticals and the health care system have on the entry of human and veterinary pharmaceuticals into the environment?

Which options for action do different professionals (doctors, veterinarians, farmers, pharmacists, drinking water providers, sewage treatment plant operators, pharmaceutical industry, patients, etc.) have to reduce the environmental risk of pharmaceuticals?

Would an ecolabel be a successful approach to reduce the environmental risk of human and veterinary pharmaceuticals?

Would an environmental classification system for human and veterinary pharmaceuticals be helpful to reduce the environmental risk of pharmaceuticals? What is the best approach? Should it be a local system or harmonized between different regions? Which stakeholders would have to be approached?

Would it be acceptable that authorization of a human pharmaceutical is denied based on the risk for the environment? Would it be possible to restrict authorization only to patient groups or indications for which no appropriate alternative treatment option is available?

Would it be appropriate to harmonize the environmental risk assessment for human and veterinary pharmaceuticals on a global scale?

Would it be feasible to take into account the environmental risk of human pharmaceuticals during benefit-risk-analysis?

What are "real" hazard concentration limits (contamination vs. pollution), and does the use and help of such products equal an environmental risk?

Endocrine disrupting effects of chemicals reproductive effects adverse health and environmental effects of nanoforms partitioning data to identify quasi persistence

To what extent can non target species be more affected than targets and consequences for the functioning of the ecosystem

To what extent will the emission of antibiotic substances to the environment by drug use or production activities provoke the development of resistance that will have a significant impact on our combat of infections?

Is the significance of the impacts of pharmaceuticals/PCPs the same for human health as it is for ecosystems? I.e., should we assess risks similarly for both?

Monitoring of disposal of pharmaceuticals and personal care products- what measures are we taking to educate the public and what options are we providing to the public to be compliant for disposing these items

Which are the biochemical, biological (natural science), technological and institutional (social science) prerequisites and limitations for an innovative re-engineering of PPCPs to easily (bio) degradable substances?

How to identify the effects of PPCPs with low dose (and long-term) exposure?

A database of concentrations of pharmaceuticals and personal care products in sewage effluent, grey water etc would be really useful.
Can we develop a removal system to eliminate the majority of the structurally diverse pharmaceuticals from sewage effluent?

What are the bioconcentration and bioaccumulation potentials of selected model compounds?

Mixture effects of PCP and occurrence of PCP?

Given the considerable benefits from pharmaceuticals and personal care products, is it really necessary to manage the risks to ecosystems? Are they almost negligible?

What really are the field effects on ecosystems?

What level will these PPCPs get into drinking source water? How would these PPCPs at their current environmental exposure level adversely affect aquatic organisms at critical life stage?
Questions taken forward to the workshop (broken down by breakout group)

BG1. Ecological effects of PPCP exposure (12)

1. What evidence is there that pharmaceuticals in the environment are affecting ecosystems and human health?
2. Are herbivorous, omnivorous and piscivorous birds and other wildlife at risk from PPCP exposures?
3. How do human and veterinary pharmaceuticals affect biodiversity and protected species? Are those effects covered by the current risk assessment?
4. What is the effect of sludge and manure-associated PPCPs on soil ecosystems?
5. What is the effect of pharmaceuticals and mixtures of pharmaceuticals on the microbial community and the ability to deliver vital ecosystem services?
6. What are the spatio-temporal cycles in ecosystem response to constant exposure of PPCPs with respect to ecosystem services and how can they be actively managed to sustain an environment capable of enduring these exposures?
7. Which trophic levels are at risk to a given class of pharmaceuticals?
8. How do non-standard effects endpoints that have been observed in organisms exposed to pharmaceuticals, such as biomarker responses, relate to ecologically important endpoints such as survival, growth and reproduction?
9. What is the environmental impact of chemicals in suncare products to marine environments? Many tons of suncare products are used each year and enter the marine environment what is their fate and do they negatively impact fish, plankton or living corals?
10. Ecotoxicological responses of marine organisms to triclosan and methyl-triclosan?
11. What effects does the use of wild plants or animals as pharmaceuticals have on the environment/biodiversity? If there are adverse effects, would additional regulation be needed?
12. What is (are) the effect(s) of multiple stressors in the receiving ecosystems?

BG2. Use of safety data and mode of action data (15)

13. How can pharmaceutical preclinical and clinical information (ADMET, side effect data, drug-drug interactions etc) be used to assess the potential for adverse environmental impacts of pharmaceuticals and pharmaceutical mixtures and customize subsequent testing strategies?
14. If the proposed approaches to leverage mammalian or target organism pharmacology and toxicology data to predict aquatic and terrestrial wildlife effects of PPCPs are promising, what data are needed to experimentally validate these potentially predictive models?
15. Can ‘omics’ and other novel technologies be used to identify pharmaceuticals and pharmaceutical modes of action that might pose a risk to the environment? If so, how?
16. Is there a correlation between dose and effect values in the environment? Do pharmaceuticals which are used at lower doses show effects at lower concentrations? If yes, which consequences does this have for the use of trigger values and the prediction of environmental concentrations?
17. Are the actions of pharmaceuticals conserved across different groups of organism?
Some have suggested use of drug development data for target species (e.g. humans) to identify potentially sensitive species/endpoints in terms of eco effects, based on degree of structural conservation of molecular drug targets. Is this reasonable? How could one demonstrate a "proof of concept"?

What endpoints both traditional as well as molecular and behavioural can be used to identify MOA?

Mechanism based testing strategy: The ecotoxicological testing of APIs for risk assessment is based mainly on standard procedures. How can we develop specific test methods, which appreciate the different modes of actions of APIs, for example as it is done for endocrine active compounds?

Why can't there be an organized research effort to use pharmaceuticals and veterinary products as molecular probes to look for homologous responses in other species to expand our basic understanding of how organisms respond to well understood chemicals?

Do PPCP behave in the environment (e.g., transport and fate, toxicity) as predicted by SARs based primarily on industrial chemicals?

Can you correlate the harmful effects of PPCPs to their structural characteristics?

How can we group pharmaceuticals and study them using representatives within an MOA to illustrate the effect of mixtures of pharmaceuticals within and across MOA on Aquatic and Terrestrial Organisms?

Pharmaceuticals are biologically active compounds with specific modes of action. How do we integrate MOA based evaluations of aquatic species into risk assessments and eventually into the regulatory framework?

The concentration of various PPCPs has required an understanding of MoA's, especially in low concentrations. Have these chemicals been truly assessed for MoA that is relevant to receiving water communities?

How does the interaction of a pharmaceutical with its receptor translate to an individual or population level effect?

**BG3. Bioavailability, uptake and metabolism (11)**

How can the BCF and BAF of ionisable organics be measured or modelled?

Do ADME characteristics in mammals predict ADME of pharmaceuticals in fish models? For example, are Vd, Cmax, t1/2, Cl values from humans predictive of those parameters in a 700 g fish or a red-eared slider turtle?

What is the bioavailability of pharmaceuticals to aquatic and terrestrial organisms, including those that are tightly bound to soil and sediment particles, and can changes in environmental conditions affect this?

What factors affect the bioaccumulation and bioconcentration of pharmaceuticals in aquatic and terrestrial systems and food chains?

What is the risk of bioaccumulation and impacts of PPCPs, particularly in human target species?

How can transformation products of active ingredients of human and veterinary pharmaceuticals be assessed?

Is it demonstrable from first principles that human metabolites of pharmaceuticals will have a lower ecotoxicity than the parent compound?
What role do pharmaceutical metabolites play in the risk posed to the environment from PIE?

Should regulatory assessments account for the influences of site specific pH on bioavailability and effects of weak acid and weak base PPCPs?

Should regulatory assessments of PPCPs account for differences in metabolism and effects of enantiomers? E.g., Why is chirality not accounted for in PPCP ERAs?

Is it appropriate to use Kow for ionisable organics, or would Dow be more appropriate as a trigger value within a regulatory context?

**BG4. Antibiotic resistance and human health (8)**

Does environmental exposure to antimicrobial residues, or to antimicrobial-resistance determinants selected for anthropogenically, promote resistance in environmental microorganisms, and create a reservoir that is then important in resistance development in human pathogens or commensals and what factors affect this?

Does resistance pass from the natural environment to the clinical environment and result in hospital acquired infections?

Is a decreased selection pressure for acquiring antibiotic resistance, i.e., lower emissions of antibiotic substances into the environment, likely to result in also a lower abundance of antibiotic resistance genes in environmental bacteria? (Or is the acquired resistance genes preserved?)

How can we assess the risks that a pharmaceutical entering the external environment promotes resistance mechanisms, of a type that would be clinically relevant, and that these mechanisms then spread to the human microflora and eventually pathogens?

Since antibiotic resistance, once developed, tend to spread all over the world, should we put most focus on managing the worst environmental antibiotic pollution sources regardless of where they are located, or should each country focus on their own backyard?

To what extent do pharmaceuticals in the environment get into food supplies and what are the implications of this in terms of risks to human health?

Are there any health effects from trace levels of PPCPs in drinking water, acting either alone or in combination?

To what extent does the personal care products affect human life cycle (in particular fertility)?

**BG5. Regulatory risk assessment and testing (14)**

Should medicines with both human and veterinary applications be assessed within a single framework to capture the ‘collective’ risk?

Should we collect the same amount of human health and environmental data on personal care products, and especially "natural" products, as we do for pharmaceuticals?

What are appropriate risk assessment processes for whole effluent and mixtures? Should the chemical-by-chemical assessment approach be abandon or does it still have an appropriate place in an assessment paradigm?

How can we determine the regulatory-level risk of these compounds in an efficient, timely manner?

What data which we currently collect are most valuable for risk assessment and what can be discarded?
Should any non-standard endpoints be included in the environmental risk assessment of pharmaceuticals?

What can be done to harmonize evaluation of risk to aquatic or terrestrial organisms from exposure to pharmaceutical residues?

Is the current standardized testing regime and environmental risk assessment methodology for pharmaceuticals protective of both humans and environmental organisms?

Is the terrestrial compartment sufficiently protected by current ERA procedures?

What would be an appropriate test for inhibition of microbial activity in the environment (besides STPs) by pharmaceuticals?

How should genotoxicity of an active ingredient be assessed with regard to environmental organisms?

How can an environmental risk assessment be conducted for pharmaceutical active ingredients that are no standard small molecule drugs (e.g. biopharmaceuticals and nanomedicines)?

Are cladoceran reproduction assays appropriate for characterizing chronic toxicity of all PPCPs?

What would be an appropriate approach to assess mixture toxicity in the ERA for human and veterinary pharmaceuticals?

**BG6. Risk management (8)**

If a drug has an adverse PBT and/or environmental risk profile what can be done to manage and mitigate the risks? Case studies?

Is green drug design feasible? How will it work? And, what are the success criteria or protection goals? What if greener drug design is not feasible?

Would an environmental classification system for human and veterinary pharmaceuticals be helpful to reduce the environmental risk of pharmaceuticals? What is the best approach? Should it be a local system or harmonized between different regions? Which stakeholders would have to be approached?

What effluent treatment methods are effective in reducing the APIs causing the highest environmental risks, at the same time 1) not increasing the toxicity of the whole effluents, 2) being economically feasible, and 3) also being able to remove other unwanted organic contaminants?

How would phasing out the use of antibiotics in CAFO’s, except in obviously sick animals, change the impact of effluent on aquatic systems?

How could the risk for the environment be taken into account in the benefit-risk-assessment for veterinary pharmaceuticals?

What would be the socio-economic consequences of restricting pharmaceutical use based solely on categorization schemes highlighting adverse environmental hazard or risk?

How should we manage the risks associated with pharmaceuticals that have environmental data gaps?

**BG7. Thresholds of concern and long-term exposure (11)**

Can threshold concentrations based on biological activity be determined that are generally protective of humans and environmental organisms?
Environmental regulations for drugs are based on a threshold of effect. There is a need for an independent and non-industry sponsored review of the supporting data and review this approach in light of "non-threshold" concerns like carcinogenicity, endocrine effects, and antimicrobial resistance.

At what environmentally relevant concentration are PPCPs causing adverse effects to aquatic organisms that can negatively affect populations and communities of these organisms?

Is it possible to get industry to share the wealth of data they have gathered over the years on the various pharmaceuticals that are likely to cause environmental concern? Are any moves being made in this direction?

Can we make more out of the available data if data transparency is increased and the data is coordinated more effectively?

What are the risks associated with long-term exposure to pharmaceuticals at low levels on ecosystems and human health based on current and projected environmental concentrations, and how can they be assessed?

What is the long-term toxicity of low concentrations of pharmacological mixtures to aquatic and terrestrial life?

What data or studies exist to show that simple acute toxicity tests provide sufficient information to assess potentially chronic exposures to PPCPs for the wide spectrum of PPCPs? What is the range of known Acute-to-Chronic Ratios (ACRs) and do these ACRs reflect different modes of action?

Given that environmental exposure is most likely to be continuous and chronic what are the appropriate endpoints to be explored in aquatic vertebrates/invertebrates and humans?

What are the gaps in current pharmaceutical and ecological knowledge that need to be filled in order to assess potential human and ecosystem effects of long-term low level exposures to pharmaceuticals?

What are the trans-generational impacts of exposures to pharmaceuticals?

**BG8. Prioritization and relative risk issues (11)**

Which pharmaceuticals and personal care products should we worry about? Which ones cause effects in the environment?

What is the best prioritization strategy to determine how the research efforts should be directed to minimize the negative effects of PPCPs on human health and ecosystems?

What would an efficient approach be for "discovery" of potential impacts of drugs, not related to their therapeutic targets, on plants, invertebrates and vertebrates without testing everything?

How do different classes of pharmaceuticals affect target species?

What is the relative contribution of hormones derived from livestock operations compared to human waste streams to the receiving environment?

What is the relative contribution of veterinary drugs to PPCPs from human sources in the receiving environment?

How can we resolve the effects of low concentrations of pharmaceuticals from the effects of the multiple other co-contaminants that are commonly encountered in real-life exposure scenarios?
How do risks from trace levels of pharmaceutical and personal care products in the environment compare to other human and environmental risks facing society, and how can we quantify these risks for comparison?

What physical-chemical characteristics distinguish PPCPs from other chemicals that results in greater or lesser concern compared to "general chemicals"?

What is the relative contribution of PPCPs to natural hormones from human sources to effects in the receiving environment?

How important is the contribution of pharmaceuticals compared to other contaminants to real-world mixture toxicity?

**BG9. Temporal and spatial variations in exposure and risk (10)**

How will environmental change affect the use and fate of pharmaceuticals and personal care products and how will this affect environmental risks compared to today?

Will rising concentrations of pharmaceutical residues as a result of decreased water use and changing precipitation patterns put these watershed ecosystems at more risk?

What are the key environmental exposure pathways for organisms (including humans) to PPCPs in the environment and are we missing any of these in current risk assessment approaches?

Is the climatic difference between north and south or between coastal and continental, humid and dry, e.g., for North America and Europe, significant for the environmental fate (and ecotoxicity) of PPCP? If so, do we need to integrate that difference in PEC or PNECs or not?

What needs to be done to extend current environmental risk assessment schemes for Europe and N. America to other geographical regions with different emission scenarios and cultural practices?

How can we effectively target which areas or regions are most at risk to health issues related to pharmaceuticals in the environment? Are these risks related to manufacturing, use, population demographics or the presence or absence of infrastructure?

What are the direct emissions of active pharmaceutical ingredients from manufacturing sites world-wide (concentrations, volumes) and what are the risks (human health and ecological) associated with such releases? How can this be better regulated?

Can more accurate partitioning models be developed for pharmaceuticals so that environmental concentration estimates are more accurate?

What are the various exposure profiles in freshwater and terrestrial ecosystems associated with sources of pharmaceuticals both human and animal?

What is the effort done to evaluate the level of pharmaceuticals and personal care product in indoor environment?

In which chemical forms do PPCPs exist in aqueous environments: metabolic by-products, environmental degradation products, or original formulations? How does pH affect their chemical structure?
4. References

