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Executive summary

The Knappe project is a FP6 SSA European project, financed by the DG research that aims to establish the state of the art of the current knowledge concerning the presence of pharmaceutical products (PPs) in the environment and to propose recommendations (priority actions) to lower this presence.

Over the duration (18 months) of the project, data concerning manufacture, consumption, occurrence, elimination, impact, regulation, and stewardship of PPs have been collected and integrated. On the basis of the findings, there is no evidence to indicate that current levels of PPs in the environment appear to be at concentrations that will result in significant environmental impact or human damage. However, there is a public concern that such residues exist and thus further cost effective measures to reduce these residues without inhibiting patient care need to be considered.

KNAPPE discussions have been valuable as a forum for an open and honest exchange of views by the stakeholders who have participated and those who have taken part are committed to continuing the dialogue to seek to come to a better common understand of the issue and so to be better placed in the future to answer questions on this topic.

At this stage, some recommendations in order to reduce the presence of PPs in the environment and hence the mitigation of the fears of the general public have been elaborated. They are presented in this report and are focussed on two main actions:

1) Advance scientific and technical knowledge concerning fate and effect of PP's

- ***Review effectiveness of current and potential STP processes for removal of PPs:*** the efficiency of wastewater and drinking water treatment processes need to be improved, either by optimising the existing systems or by the application of improved technologies.
- ***Increase knowledge of the environmental effects of PP's:*** further work is needed to establish the ecological relevance of sub-lethal responses, particularly the relevance of non-standard endpoints, the significance of metabolites and transformation products and to investigate how the impact of mixtures could be evaluated.

- ***Develop intelligent testing strategies for chronic toxicity assessment:*** intelligent testing strategies need to be developed to improve the assessment of chronic toxicity. This should include assessments of mode of action and utilise emerging data from ‘omics’ technologies.
- ***Further investigate fate of PP's in STPs:*** the interaction between PPs and solids, particularly in wastewater treatment plants needs further study. In particular, a better understanding of whether residues are permanently bound to solids or if they can be released back into the environment.
- ***Evaluate role of environmental monitoring in risk assessment:*** there is a need to improve monitoring strategies. A priority list of PPs should be established, where possible spot sampling should be replaced by integrated methods and there should be a central repository for monitoring data using a standardised format.
- ***Evaluate practicalities of adopting a "green pharmacy":*** the development of ‘greener’ pharmaceuticals needs to be stimulated. This could be done by providing an incentive of increased patent life, or incorporating the outcome of the environmental risk assessment into the drug approval process.

2) Control of emission of PPs into the environment

- ***Evaluate effectiveness of classification schemes:*** the Swedish system for the environmental classification of pharmaceuticals is a good method for providing information to health professionals and patients. A review of the value and benefits of this scheme on PPs environmental classification is currently ongoing. We recommend that a general European framework for environmental classification should be developed which could be adapted from country to country in order to take into account the specificity in medical practices and the drug consumption of each country.
- ***Unused medicines management:*** ‘Take Back’ schemes for unused medicines represent one of the simplest ways to reduce inputs of PPs to the environment. We recommend that quantitative information should be obtained on the efficiency of existing schemes and that each Member State should then seek to adopt best practices for such schemes, including the provision of information to patients. A European guideline could be very useful.

- ***Evaluate methodologies to better inform public***: strategies to enhance public awareness of the impact of pharmaceuticals in the environment need to be developed in order to stimulate a more responsible approach to the use of medicines and their appropriate disposal.
- ***Evaluate need for policy framework reform***: The current policy framework is considered sufficient to deal with the issue of PPs in the water environment although implementation could be improved e.g. take back schemes. Environmental risk assessment procedures need to be kept up to date and should be applied to existing, as well as new medicines. The upgrading of wastewater treatment systems might be an option to reduce environmental residues further but this needs to be considered with respect to cost (both financial and environmental) risk and benefit.

1. Introduction

The Knappe project proposed to make an overview of the knowledge currently available in the literature at national and international levels. It aimed to collect as much as possible of the information concerning the whole life cycle of pharmaceutical products (PPs) from their manufacture to their release into the environment. This data collection took into account:

- Production,
- Prescription and distribution practices from country to country,
- Environmental occurrence and fate,
- Elimination processes (sewage treatment plants, waterworks) and their efficiency,
- Impact on aquatic and terrestrial organisms (including humans),
- Policy instruments, with a view to proposing a possible future action programme regulatory directives and other legislative initiatives) to prevent and limit pollution of water with PPs

The project mainly focussed on pharmaceutical products used for human healthcare and did not consider veterinary products.

The collected information has been reported in several deliverables (available at www.knappe-eu.org).

The final objectives of the project were to integrate and interconnect the collected data and information in order to (Figure 1):

- Identify the gaps in the scientific knowledge,
- Define possible actions at each step of the life cycle and propose recommendations for reducing the presence and impact of PPs in the environment.

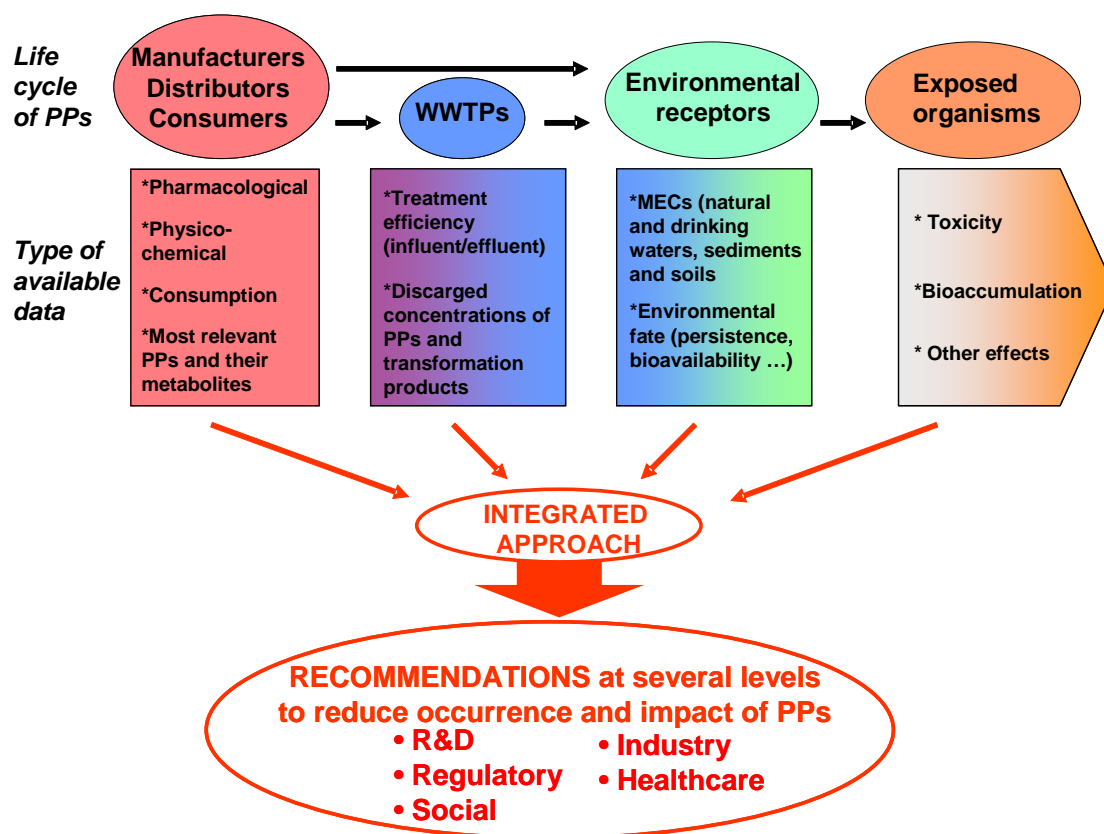


Figure 1: Integrated management within Knappe project

In the first part of this deliverable, the main key points of the topic are reported while in the second part, a series of recommendations is presented.

2. Main Key points

2.1. Properties of Pharmaceutical Products

Pharmaceutical Products (PPs) or Active Pharmaceutical Ingredients (APIs) are complex molecules with a wide range of functionalities and physicochemical and biological properties. Most of them are polar compounds. They are developed to have a range of biological activity (especially in human body). They are mainly small molecules (200 to 1000 Da) and are considered as “micro-pollutants” because their concentrations are found in the range of $\mu\text{g/L}$ to ng/L in aquatic environments (wastewater, surface water, ground water).

PPs often have basic or acidic functionalities, sometimes even within the same molecule. Under different environmental conditions (e.g. changes in pH), PPs can be neutral, cationic,

anionic, or even zwitterionic. As a consequence, the environmental fate of each PP will depend on a range of processes (including adsorption, absorption, and solubilisation), and is determined by its unique combination of physical and chemical properties. A “typical” PP does not exist.

Furthermore, in environmental studies, PPs are often described by putting forward pharmacological criteria such as:

- ***Their purpose and biological activity*** (e.g. antibiotics, analgesics, anti-neoplastics, anti-inflammatory substances, antibiotics, anti-histamines, X-ray contrast media),

- ***Their chemical structure***: this is mainly used for the active substances within sub-groups of medicines, e.g. within the group of antibiotics such as β -lactams, cephalosporins, penicillins or quinolones. In this case, one may expect that the compounds can be treated as groups with respect to chemical behaviour. However, even small changes in the chemical structure may have a significant impact on solubility and polarity as well as other properties that govern their environmental fate.

- ***The mode of action*** (MOA) e.g. anti-metabolites or alkylating agents within the group of cytotoxics/anti-neoplastics. In the case of classification according to MOA, chemical structures of molecules within the same group can be very different and therefore their environmental fate can differ, too. In this case, compounds cannot be handled as a group with respect to environmental issues e.g. anti-metabolites or alkylating agents within the group of cytotoxics/anti-neoplastics.

On the other hand, it is crucial to consider that a PP can undergo structural transformation at several stages in its life, and can be the precursor of by-products (Figure 2).

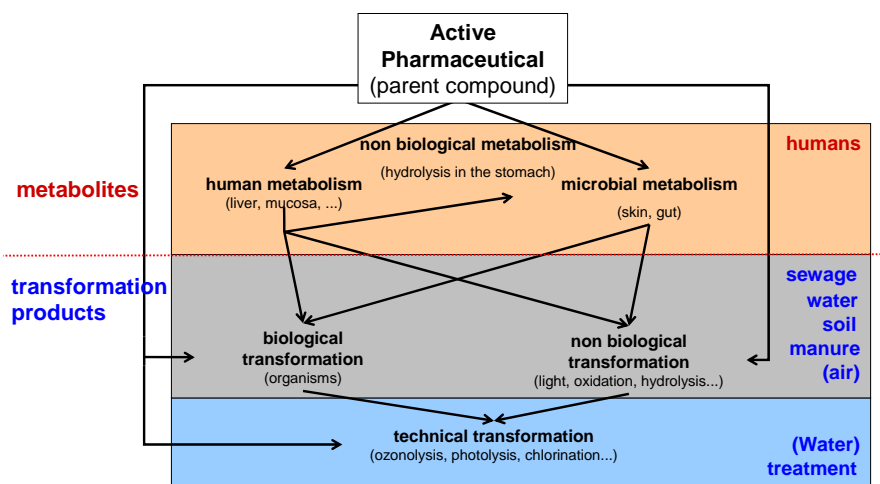


Figure 2: Nomenclature of PPs by-products (Kuemmerer, 2008)

PPs can be:

- metabolized by the human body to a variable extent. This could be due to micro-organisms in the gut or by human enzymes such as cytochrome-linked oxygenases. In this case, the resulting substances are called *metabolites*,

- bio-transformed by organisms such as bacteria and fungi or chemically transformed by a variety of biotic and non-biotic processes after its introduction into the environment. Structural transformations may also be a result of effluent treatment. In this case, the expression *transformation product* will be employed for the resulting substances.

Currently there is much confusion in the literature about this and we recommend that these terms should be used consistently in order to prevent confusion in the assessment of the fate and risks connected to the presence of these molecules in the environment.

2.2. Consumption and use

There is a lot of variation in the practices and mode of consumption of pharmaceuticals from country to country. For example, data from France reflect the total amount consumed including those quantities sold without prescription - freely over the counter (OTC-drugs), while the consumption data from Germany, Poland, Spain and the UK (England and Wales)

do not include OTC-drugs. Consequently, it is very difficult to obtain representative data about the worldwide use of pharmaceuticals.

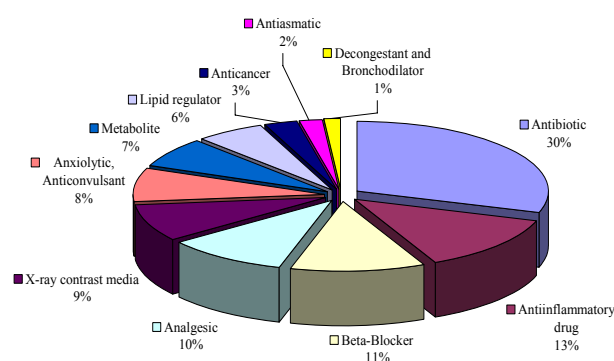
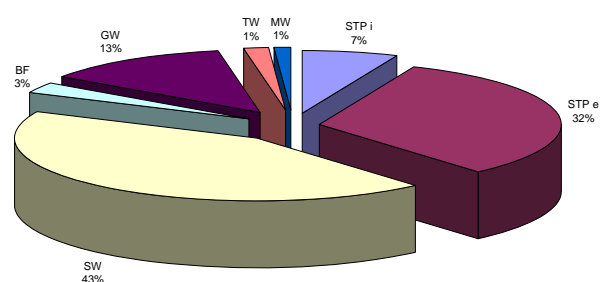
The source of emission of PPs in the environment varies, but it is generally accepted that emissions from pharmaceutical manufacturing are negligible especially in Europe and the North America (in Asian countries concentrations discharged for single compounds can be up to several mg L⁻¹). On the contrary, excretion by patients in private households has been found to be the most important source of discharge in the environment. Furthermore, although PPs are found in hospital wastewater at higher concentrations than in municipal sewage, the total load from hospitals is much lower because of the small proportion of effluent from hospitals in municipal effluent in developed countries.

2.3. Occurrence and Fate in the Environment

Studies describe the occurrence of pharmaceutical products in all aquatic environments (waste water, surface water, ground water, drinking water) though wastewater and surface water have received the most attention.

Moreover, all pharmaceutical classes have been studied. More than 45000 records have been identified. However, these deal with only 180 out of more than 4000 active pharmaceutical ingredients sold all around Europe. It is notable that one third of these records concerned only 10 molecules (diclofenac, carbamazepine, clofibric acid, ibuprofen, bezafibrate, sulfamethoxazole, trimethoprim, phenazone, ketoprofen, roxithromycin).

The concentrations in surface waters and effluents from STPs are mostly in the ng/L range with a few large volume products appearing in the µg/L range. Less information is available



for the concentration in drinking water and marine water. There is little information is available concerning occurrence, fate or activity of metabolites and transformation products.

PPs enter the environment mainly via wastewater after treatment. The behaviour of PPs in wastewater treatment plants is very dependent on the properties of the compound and the applied treatment process: the removal efficiency can vary from 0 to 100% (Miao et al., 2003; Vienoa et al., 2007). Advanced treatment processes can be employed to improve the elimination rate of some PPs. Even where PPs are resistant to STP treatment and enter surface waters, they they may still be removed through processes such as photodegradation, sorption, or biodegradation. Little is know about the distribution of PPs between the solid and liquid phases in the STP (few studies have been performed on sludge and sediments).

2.4. Effects/impact

Effect and/or impact of PPs on aquatic or terrestrial organisms are amongst the main sources of concern that lead to public interest in the presence of PPs in the environment. Literature is not very abundant on this topic.

The majority of the data show that acute effects on adult aquatic organisms are not expected to occur especially at the current environmental concentrations. Indeed, for most of the investigated PPs, the chronic LOEC is higher than the maximal concentrations found in STP effluents (environmental concentrations are more than 10000 times lower than the therapeutic doses).

On the other hand, most of the ecotoxicity studies have been measured acute toxicity and there are relatively few data available on the effects of chronic exposure. This is an important data gap in order to understand the behaviour of PPs in the environment (bioaccumulation, bioconcentration), though some chronic data is now being generated through EMEA ERA requirements, and through industry gap filling initiatives.

Finally, most impact investigations have been based on single compounds. But mixtures (of all micropollutants, not only PPs) have been shown to cause different effects than single

compounds alone. Moreover, there is very little information on the impact of metabolites and transformation products.

2.5. Policy framework

Micropollutants are often managed by regulations, especially in term of surveillance and control in different water bodies. Pharmaceutical products are currently not specifically controlled in these regulations at the European level. The Water Framework Directive (WFD) is the key directive for surface water. A list of priority substances has been identified in which PPs are not included. The Drinking Water & Groundwater Directives do not recommend monitoring PPs as key substances. In the Urban Wastewater Treatment Directive (end-of-pipe), PP removal is not required. Finally, the Sewage Sludge Directive does not define set limits set for PPs in urban sludge.

In conclusion, a general acceptance that there is currently no evidence of a problem: current levels of PPs in the environment do not appear to be at concentrations that will result in significant environmental damage. However there is public concern/fear that such residues exist and thus further cost effective measures to reduce these residues without inhibiting patient care need to be considered. The next section will present a short list of recommendations identified as being able to contribute to this objective.

3. Recommendations

The presence of Pharmaceutical Products in the environment is the responsibility of all actors involved in their life cycle from manufacture to exposure to aquatic and terrestrial organisms.

In order to reduce the occurrence of PPs in the environment, actions need to be taken, now. In most cases, the identified measures will not require any cross-sector agreements but their efficiency will depend on a cooperative approach. Moreover, work on the basis of shared responsibilities should be promoted, in particular, to minimize the costs and to promote innovation.

In the frame of above, five spheres of actions (Figure 3 + regulatory sphere), corresponding to the main actors in the life cycle of PPs, can be defined and recommendations are proposed according to these spheres of influence.

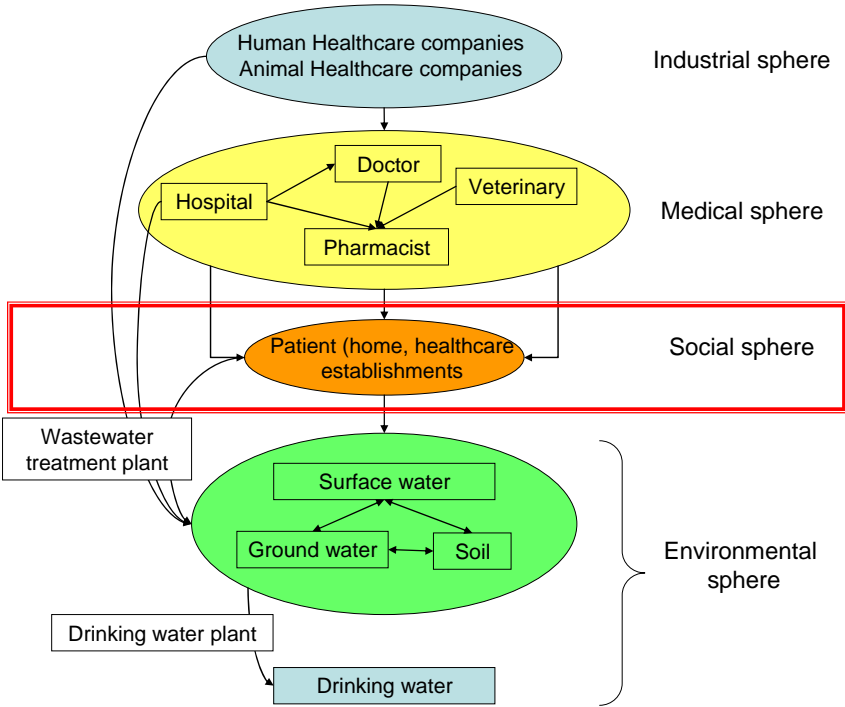


Figure 3 : Life cycle of PPs and the associated actors gathered in different spheres. The regulatory sphere should complete the figure

As mentioned previously, all data show that the pharmaceutical manufacturing (apart from in some developing countries) is not the main source for the presence of PPs in the environment.

The main source of pharmaceuticals in the environment is the result of patient use (either at home or in a healthcare establishment).

In the following proposed recommendations, the objective is not to prevent the treatment of patients with pharmaceutical products, but to mitigate the environmental impact of this use. Considering the patient as the central actor, we can define these recommendations as:

- **pro-actions**: actions that have to be taken in order to prevent the introduction of PPs in the environment by acting upstream from the use by the patient (preventive approach),
- **post-actions**: actions that have to be taken in order to treat the consequences of the release of PPs in the environment by acting downstream from the use by the patient (curative approach),
- **actions**: that have to be taken at the same time as the use of PPs (day to day approach).

According to these three classes, recommendations can be addressed to one of several spheres in an independent manner or within a collaborative process. In the following, we focus on the 10 most relevant actions consisting of:

Advance scientific and technical knowledge concerning fate and effect of PP's

- *Review effectiveness of current and potential removal STP processes*
- *Increase knowledge of the environmental effects of PP's*
- *Develop intelligent testing strategies for chronic toxicity assessment*
- *Further investigate fate of PP's in STPs*
- *Evaluate role of environmental monitoring in risk assessment*
- *Evaluate practicalities of adopting a "green pharmacy"*

Control of emission of PPs into the environment

- *Evaluate effectiveness of classification schemes*
- *Unused medicines management*
- *Evaluate methodologies to better inform public*
- *Evaluate need for policy framework reform*

Consequently, 10 thematic sheets are proposed by indicating firstly the recommendation box and in the following the rationale and the context.

Increase knowledge on environmental impact and effect

Recommendation: Further work is needed to establish the ecological relevance of sub-lethal responses, particularly the relevance of non-standard endpoints, the significance of metabolites and transformation products and to investigate how the impact of mixtures could be evaluated.

Over the past ten years, a large body of data has been generated on the effects of pharmaceuticals on organisms within the environment. Around 20,000 study endpoints for both human and veterinary pharmaceuticals are available. The data include both acute and chronic endpoints and the top three study organisms are fish, water flea and other small crustaceans. The top three drug classes studied are cholinesterase inhibitors (used in veterinary medicine), lysozyme inhibitors and antiscabies agents (e.g lindane). When all data are considered, the vast majority of studies indicate that, in general, pharmaceuticals are not toxic to aquatic organisms. A small proportion of compounds are however highly toxic to some organisms and endpoints. The interpretation of the published ecotoxicological data in terms of its environmental significance shows that i) acute effects of pharmaceuticals on the environment are unlikely; ii) standard chronic effects are possible for some substances at environmentally realistic concentrations; and iii) subtle effects (not covered in standard toxicity investigations) are also possible for some pharmaceuticals at environmentally realistic concentrations. The ecological relevance of these subtle effects is however not known.

A number of *non-standard ecotoxicity studies* have been performed on pharmaceuticals (Delange, 2006; Flippin, 2007, Quinn, 2008; Pounds, 2008). These studies have involved the use of invertebrates and fish and have looked at a range of new endpoints including effects on nest holding, egg production, heart rate, activity and feeding rate and behaviour. Several of these ‘novel’ effects can occur at environmentally realistic concentration levels.

Thus, existing environmental toxicity assays and end points are not necessarily suitable for measuring the impact of PPs and it is important to determine whether or not the results of new endpoints should be of concern in the assessment of the risks of PPs in the environment. These novel assays need to be developed and correlated with standard endpoints addressing population effects so that their relevance can be assessed.

One further important element needs also to be considered: environmental exposures are never due to a single compound but rather a mixture of pharmaceuticals as well as many other household chemicals or other water contaminants. Current procedure consists of considering the effect of a mixture as an addition of the effect of the constituted mixture compounds. However, there is still some debate on the effects of mixtures and the assessment of their effects needs to be further investigated either by using modelling or *in vitro* or *in vivo* studies.

Finally, there is an important need for information on metabolites and/or transformation products of PPs. Indeed, with the exception of a few drugs, limited information is available in the public domain on the ***ecotoxicity of metabolites and transformation products***. Data are available on the ecotoxicity of pesticide transformation products that provide useful information on which factors make a transformation product more ecotoxic than the parent compound. The majority of pesticides transformation products is less toxic or has similar toxicity to their associated parent compound. However, some are more than 3 times more toxic than the parent compound. These observed increases can be due to a number of reasons:

- 1) The uptake of the transformation product into organisms is greater than for the parent compound, due to either an increase in lipophilicity or a change in dissociation or both;
- 2) The transformation product contains the active moiety of the parent compound;
- 3) The transformation reaction results in the introduction of a toxic moiety which is not present in the parent compound.

Using the above knowledge, if the structure of a metabolite or transformation product of a pharmaceutical is known, it is possible to identify which substances are likely to be more toxic than the associated parent compound. The lipophilicity and dissociation behaviour of a molecule can be estimated using quantitative structure-property relationships. If the active moiety (or pharmacophore) of the parent compound is known, then a quick visual assessment of the transformation product can indicate whether this moiety is present in the transformation product molecule. Several approaches are available to identify whether a new toxic moiety has been introduced during the transformation reaction. These approaches generally use structural alerts that are associated with a range of environmental models of action. If the transformation product contains one of these structural alerts but this alert is not present in the parent compound, then the transformation product may be more toxic than the parent compound.

Intelligent testing strategies for chronic ecotoxicology studies

Recommendation: Intelligent testing strategies need to be developed to improve the assessment of chronic toxicity. This should include assessments of mode of action and utilise emerging data from 'omics' technologies

Generally PPs do not exhibit acute toxicity to aquatic and terrestrial organisms where classical end-points in conventional ecotoxicity tests are used. A number of studies has shown that extrapolation of these tests to assess chronic toxicity is not always representative of the possible real long term effect. Assessment on the long-term effects of PPs on aquatic organisms is a relatively new phenomenon with the majority of available data being derived from standard acute tests (chronic data is now being generated at the behest of the EMEA ERA guidelines). Extrapolation approaches (e.g. use of acute:chronic ratios) and QSARs can be proposed for estimating chronic ecotoxicity values but some preliminary studies concluded that currently available QSAR approaches and the application of typical acute/chronic ratios for estimating chronic toxicity from acute toxicity are probably inappropriate for use on all classes of pharmaceuticals (ACRs are protective for most pharmaceuticals; some notable exceptions have been described). Further development work is therefore required in this area.

The Intelligent Testing Strategies (ITS) approach is being developed for in vivo chemical testing. This approach involves using all the available knowledge about, and the mechanism of action (MOA) of manufactured chemicals (e.g. pharmaceuticals and plant protection products), and the specific target sites they are intended to interact with in living organisms (e.g. proteins such as enzymes, ion channels, receptors and protein transporters), in order to design efficient testing strategies using the most appropriate test species. This approach to aquatic ecotoxicity testing includes:

- gathering all available MOA information on the primary pharmacological/toxicological activity (and any additional toxicity MOAs) of the chemical of interest in the target species as well as in mammals;

- making use of non-traditional sources of biological information, especially the growing biomedical and ‘omics’ electronic databases on zebra fish, marine invertebrates and other non-mammalian species;
- measuring biomarker responses (e.g. vitellogenin), for read-across purposes or setting test concentrations. Population-relevant endpoints such as survival, development, growth and reproduction, should be used to generate No-Observed Effect Concentration (NOEC) values or to calculate Predicted No Effect Concentration (PNEC) values;
- using acute interspecies sensitivity ratios (ISRs) cautiously for algae, crustaceans or fish, since the available data suggest they are of limited value for ITS application. This may be due to acute high levels of exposure inducing different MOAs of the chemical compared with chronic low level exposures. However, it should be noted that for a wide diversity of chemicals, acute data do not reliably indicate the MOA for aquatic organisms.

As identified by ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals; <http://www.ecetoc.org>) improvement is required in these strategies and approaches to this are:

- Critical review of data (especially chronic studies) from a wider range of chemicals, including chemicals where the mammalian MOA is less specific;
- Development aquatic plant ADME (absorption, distribution, metabolism, and excretion) models to understand key biotransformation enzymes;
- Strengthen the use of small invertebrate models
 - investing in biological understanding (including genomics, proteomics and population responses) in the commonly used freshwater and marine invertebrate species (including both arthropods and non-arthropods)
- For animal welfare reasons, minimization of the need for *in vivo* fish bioconcentration testing
 - developing *in vitro* fish protocols for chemical metabolism;
 - develop a small-scale invertebrate bioconcentration test method; support risk assessments of endocrine disrupters;
 - develop a database of the normal (baseline) range for developmental and reproductive endpoints in aquatic organisms measured across different laboratories;
- Capitalization on the learning from zebra fish biomedical and ‘omic’ research;

- establishment of a publicly available database on zebrafish ADME and toxicity information.

Interaction of PPs with solids

Recommendation: The interaction between PPs and solids, particularly in wastewater treatment plants, needs further study. In particular, a better understanding of whether residues are permanently bound to solids or if they can be released back into the environment.

PPs typically enter the aquatic environment after passage through a STP. The efficiency of the process for a targeted compound is measured by the ratio of the concentration in the effluent by the concentration of the influent. A yield of elimination can be then established. However, this does not necessarily provide information on degradation. Little is known about the distribution of PPs between the liquid and solid phases in the STP. Sludge generated in wastewater treatment process can be a major sink for some pharmaceutical products. The land application of sewage sludge can therefore potentially reintroduce PPs into the environment. Knowledge of the distribution of PPs between solid and liquid phases is needed.

Techniques (including Soxhlet extraction or sonication (Lindberg, 2005), pressurized liquid extraction (PLE) or microwave-assisted extraction (MAE) (Nieto, 2007; Buyuksonmez, 2005) are currently available and already used for the extraction of pharmaceuticals from solid phases such as sludge and soil. However, their application in studies of the interaction between PPs and biosolids (in STPs) and the studies on real sewage treatment plants are very limited and need to be developed. Further, once in the environment PPs can undergo several biotic or abiotic transformations and interactions with sediments in surface water systems has been sparsely studied to date. Binding to suspended or dissolved organic matter has great importance in terms of bioavailability and accumulation of PPs in the solid or liquid environmental phase. The importance of the concentration and nature of dissolved and suspended matter is poorly understood, especially for trace contaminants, and in this context risk assessments assuming the worst case scenario of 100% bioavailability may grossly overestimate the risk posed by individual compounds.

Monitoring strategies

Recommendation: There is a need to improve monitoring strategies. A priority list of PPs should be established, where possible spot sampling should be replaced by integrated methods and there should be a central repository for monitoring data using a standardised format.

In spite of considerable progress in the development of laboratory-based methods, reliable monitoring of pharmaceutical products is currently difficult to achieve because of a lack of suitable sampling methods. Most monitoring uses infrequent spot (bottle or grab) water samples and this does not provide a representative picture of levels of PPs where concentrations fluctuate in time due to factors such as variable inputs or weather events. There is an urgent need to make use of more representative sampling methods such as continuous and time- and flow-weighted sampling devices or passive samplers.

The reliability of risk assessments depends on not only sound estimates of concentrations in the aquatic environment but also on reliable toxicity data. It is currently **not possible to use direct toxicity assessments for monitoring individual compounds** in the environment, and measuring concentrations of individual compounds in organisms is difficult and expensive. Where compounds are present in mixtures, interactions (e.g., antagonism or synergism) can occur. Furthermore, in the field, compounds are present along with suspended solids and dissolved organic materials (e.g., humic and fulvic acids) that affect bioavailability.

There is a need to highlight the difficulties faced in monitoring this vast range of chemicals in the various environmental compartments and highlighted the paucity of data currently available. It was agreed that within existing, and projected, monitoring budgets it would be impossible to investigate all PPs, and there **is a need for a rationale for identifying those of highest concern**. Others could be treated as of much lower priority. Compounds used in very small amounts (e.g., some anti-cancer drugs used in kg per year) could be omitted. A suggestion was to use one compound as a surrogate for a set of others on the basis of similar physicochemical properties or pharmaceutical mode of action, but it was recognised that large uncertainties were associated with this approach. Another approach to reducing monitoring

efforts would be to identify a set of sampling sites that are representative of the various types of STPs; though again it was recognised that there can be great variation in efficiency between STPs of similar design but at different locations. A better understanding of the efficiency of different types of STP in removing PPs is needed with a view to designating representative monitoring sites in the future. It was recognised that there is a need to develop appropriate biological assays to support risk assessments for these compounds that exhibit a wide range of biological activities. This would further help to focus monitoring efforts.

It was also agreed that currently data from much of the monitoring activity reported in the scientific literature is not suitable for use in risk assessments or in the development of models, and is of limited use to the wider end user community. This could be avoided by the establishment of a central repository for monitoring data. This should use a well defined standard format for both chemical and biological data, and the quality of data should be checked before inclusion. This could then incorporate information from a wide range of sources including routine regulatory monitoring and academic research. The NORMAN (Network of Reference Laboratories for Monitoring Emerging Pollutants; www.norman-network.net) project data base provides a useful basis for the development of such a repository for monitoring data for PPs. A uniform format would facilitate the development of predictive models (based on e.g., QSAR or LSER), the design of intelligence led monitoring and biological testing. This would reduce animal testing and need for extra water monitoring activity, shorten the time necessary for risk assessments for registration purposes, and thus save money. As data were accumulated in such a data base it would be possible to refine existing models. Lastly it was thought that a post registration scheme for reporting adverse environmental effects of PPs would focus monitoring efforts where needed. However, it is difficult to identify who should fund such a data base.

Improvement of PPs elimination processes

Recommendation: the efficiency of wastewater and drinking water treatment processes need to be improved, either by optimising the existing systems or by the application of improved technologies.

Municipal wastewater is one of the main routes introducing PPs into the environment, and as a result, much of the research effort has been on the occurrence and fate of those compounds during the wastewater treatment processes. Studies have shown that ng/L to µg/L concentrations for many PPs are commonly found in effluent, indicating an insufficient removal of those contaminants using current wastewater treatment techniques. Moreover, drinking water treatment works are also in some cases inefficient in the removal of some PPs, and trace levels of some of these compounds can be found in drinking water. Whilst this could be more important in the future because increases in per capita consumption, expanding population, expanding potential markets, patent expirations, new target age groups, inverting age structure in the general population and new use for existing drugs, there is no evidence to suggest that these very low levels pose any risks to human health. However, despite the evidence indicating a lack of risk to human health, the presence of PPs in drinking water has been a cause of public concern. However, this will need to be weighed against the potentially very high cost of removing trace levels of PPs (and all other pollutants) from drinking water. Thus, there is a need to evaluate the cost/benefit of improving current efficiency of wastewater and drinking water treatment. Two alternatives can be proposed: improvement of current biological processes or development of new technologies. The latter include a number of promising end-of-pipe technologies, which will allow efficient treatment of PPs, are under development using pre- or post-treatment, such as ozonation, activated carbon, UV light or nanofiltration. However, their use will increase the costs (to be assessed) of the treatment, and in some cases (e.g. Advanced Oxidation Processes) there is a risk of introducing to the environment transformation products that could be more toxic than the parent molecule. Consequently, the development of such technologies should be accompanied by toxicological and ecotoxicological investigations. Another possibility is to improve existing wastewater treatment systems by optimisation of key parameters. Indeed, it has been shown that the

removal efficiency varies in relation to sludge retention time (SRT), hydraulic retention time (HRT), and reactor configuration.

When considering sewage and drinking water treatment processes it is important to bear in mind that PPs are present at much lower concentrations than many other compounds such as those used in household cleaning and some personal care products. This is particularly important where a treatment process may produce potentially toxic degradation products. Attempts to reduce trace levels of PPs may have deleterious side effects that potentially pose a much greater threat to the environment and human health than the trace levels of PPs that the process was designed to reduce.

Drug development: Green Pharmacy

Recommendation: The development of ‘greener’ pharmaceuticals needs to be stimulated. This could be done by providing an incentive of increased patent life, or incorporating the outcome of the environmental risk assessment into the drug approval process.

To prevent the contamination of water bodies and consequently the possible risks for humans and the environment, PPs should ideally be degraded completely and as quickly as possible, or transformed into environmental friendly compounds. This approach, however, is very ambitious since active pharmaceutical ingredients rely upon their specific chemical structure to exhibit the desired biological activity and must demonstrate adequate stability and acceptable shelf life. Stability in the human body generally also means stability in sewage treatment plants and in water bodies.

Efficacy and good environmental properties do not necessarily represent a fundamental contradiction for a medicinal product. Both can be optimised by a specific molecular design. The challenge for the pharmaceutical industry over the next decades will be to design new greener drugs in such a way that their lifetime is sufficient for their use but short enough under environmental conditions (i.e. a suitable balance between stability and biodegradability). Nevertheless, it is important to note that, since the potential for degradation of pharmaceuticals greatly varies across their life cycle depending on environmental conditions (e.g., pH, temperature, redox conditions, bacteria and enzymes present), stability during the application phase and degradability thereafter are not necessarily mutually exclusive. There is a need for closer contacts between those working in the area of “Green Pharmacy” and the medicinal chemists working in the pharmaceutical industry on the development of novel active compounds.

As highlighted in the Start Project (<http://www.start-project.de/index.htm>), the development of green pharmaceuticals can be promoted in particular by research and development, on the one side and regulatory incentives, on the other side.

1) **Research and development:** in particular drug design needs to take into account the following parameters:

- *Life Cycle Assessment* (LCA). This is an environmental management tool used to examine, identify and evaluate the environmental implications of a material, process, product or system from creation to end-of-life, encompassing extraction and processing of raw materials, manufacturing, transportation and distribution, use and final disposal. LCA determines inputs and outputs at each stage of the lifecycle, and aims to provide recommendations of how environmental improvements can be made.

- *Cost-Benefit Analysis* (CBA) can be used to estimate the value of the benefits and costs of implementing approaches to minimize the environmental impacts of PPs to pharmaceutical companies to establish whether they are worthwhile. Shifting the CBA in favour of the pharmaceutical companies may be a key factor in furthering the implementation of approaches by pharmaceutical companies to minimize the impacts of pharmaceutical products throughout their lifecycle.

2) **Change of the legal frameworks:** this could generate incentive instruments able to foster the development of green products in pharmaceutical companies. One such instrument could be the *extension of patent terms* exclusively for green active ingredients from the current 20 years to for example 25 to 30 years. This would increase economic security for industry when pursuing a green product policy and would support the development of environmentally compatible active ingredients up to readiness for marketing. For this to be effective there would need to be transparent and agreed criteria to define what was meant by a ‘green’ active ingredient. On the other hand, there should also be consideration for requiring generic drug manufacturers to conduct additional environmental studies and provide updated environmental risk assessments as drug patents expire and market volumes significantly increase. It is not clear from the current regulatory processes that the generics are being asked to provide an ERA.

Finally, during the *medicine market authorisation process*, several environmental risk assessment studies have to be performed but according to the current European legislation their results are not parameters for rejection of authorization. Giving more importance of PPs environmental properties in the market authorisation process could be a stimulus for developing green products. Different possibilities can be envisaged. The following one has been stated in Start project: “A model could be, in a first phase, to generally limit (for example

to ten years) the authorisation term for active ingredients for which an environmental risk is determined. In a second phase, the authorisation could then be rejected for environmental reasons if there is an already authorised, more environmentally compatible, and therapeutically equivalent alternative to the active ingredient in question. Only in a third phase, will authorisation be denied if an active ingredient represents an environmental risk. Whether the favourable environmental properties exist only incidentally in the active ingredient or whether the attempt”

Classification of PPs of concern

Recommendation: The Swedish system for the environmental classification of pharmaceuticals is a good method for providing information to health professionals and patients. We recommend that a general European framework for environmental classification should be developed which could be adapted from country to country in order to take into account the specificity in medical practices and the drug consumption of each country.

More than 3000 active pharmaceutical ingredients are sold all around Europe and only about 200 molecules have been found in the environment. As already mentioned, data are still missing to establish clearly the consequences of the presence of these products for aquatic and terrestrial organisms. However, some information (complete or partial) is available dealing with the environmental behaviour of PPs. This information needs to be disseminated in order to promote a more environmental use of pharmaceutical products. Of the multiple possible approaches that can contribute to it, source control is seen as having the capacity of delivering important results. Source control includes targeting “hot spots” (emission sources), but also actively influencing consumption volume and compound choice. Compound choice, i.e. opting for the environmentally friendly choice in case of alternative compounds being available with comparable effectiveness, can be addressed through classification and labelling schemes.

Several classification schemes (Sweden (Ågerstrand, 2008), Canada (Sanderson, 2004), Netherlands (de Voogt, 2008), Italy (Zuccato, 2006), France (Besse, 2008)) have been proposed in the literature yielding several lists of PPs of priority concern. Unfortunately, there is not a consensus on the criteria taken into account to establish these lists. Moreover, each country has its own particularity in terms of for instance medical practices and consumption, which explains the difference between the lists from one country to another.

The establishment of an international classification system for pharmaceuticals with country-adapted versions (as already in place in Sweden) would be an important step. A possibility would be to have an environmental classification for all substances available on the market. As for the Swedish model (Stockholm County Council scheme), the system could be based on an evaluation of both the **hazard** (its inherent ability to affect the environment, based

on biodegradability (related to *persistence* in the environment), potential for *bioaccumulation*, and *toxicity* to aquatic organisms (called “PBT assessment”) and the *associated risk*, i.e. an assessment of the *probability* that adverse effects will occur and of their possible extent, based on the current use of the pharmaceutical product.

Our recommendation would be to evaluate existing schemes (a current review of the value and benefits on environmental classification of the Swedish model is ongoing), and on the basis of this create a general European framework for such a classification which could be adapted from country to country in order to take into account the specificity in medical practices and the drug consumption of each country. As a preliminary step, a first evaluation of the benefit of existing systems will be required (work already in progress). This kind of classification will require the involvement of the main stakeholders, in particular manufacturers (availability of data on toxicity of PPs contained in authorization dossier), national and international Medical Products Agency (data on consumption), local and national authorities.

This should increase the awareness of people and may be able to lead to a change in prescribing habits to the benefit of the environment without detriment to the patient. In parallel to the establishment of such a classification, further studies need to be carried out in order to map these changes and to check its real potential for changing the mentality of people.

Unused medicines management

Recommendation: ‘Take Back’ schemes for unused medicines represent one of the simplest ways to reduce inputs of PPs to the environment. We recommend that quantitative information should be obtained on the efficiency of existing schemes and that each Member State should then seek to adopt best practice for such schemes, including the provision of information to patients. A European guideline could be very useful.

Unused medicines make a small contribution to the residue levels of pharmaceuticals in the environment. If the unused medicine is returned to the pharmacist or disposed into household waste that is subsequently incinerated or sent to a secure landfill site, then entry to the environment is minimal. The earlier method of disposal, by flushing into the toilet, which could result in releases to the environment, is no longer recommended. In the European Union, the recently amended Directive on human pharmaceuticals requires all Member States to establish collection systems for unused medicines. In addition the EMEA Guidance Document on Environmental Risk Assessment of human medicines recommends that for all medicines, the patient information leaflet should contain the following general statement - *“Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.”*

In this context, the implementation of **take-back schemes** was put forward as the most popular risk management strategy for pharmaceuticals in the environment. They are seen as a positive management response because disposal of unused and expired medicine seems like a logical, easy portion to remove from the environmental loading.

Actually, 20 European countries (out of 28 countries surveyed) have a drug take-back scheme in place. Seven countries (Bulgaria, Cyprus, Greece, Latvia, Malta, Romania and Slovenia) however have no scheme and no information is available for Luxembourg. Eleven of the schemes in place are managed by pharmacies, six are co-ordinated nationally and five locally. The majority of the returned material is incinerated.

Quantitative information on the performance of the existing drug take-back schemes is not readily available for many countries (recovery rate of up to 80% in France, 75% in Sweden) and an in-depth assessment of scheme effectiveness (estimated recovery rate of unused/expired drugs) **is missing and needs to be improved.**

Networking of pharmaceutical industries, pharmacists, doctors and patients should be improved to encourage people to take back unused or expired PPs to the pharmacy. High levels of public awareness and education on the environmental consequences of the disposal of unused/expired drugs are key for the success of such schemes and need to be implemented as well as in medicine/pharmacy training than at a public scale with advertising, brochure and permanent campaign.

Management of expired and unused medicines is generally well documented, but there are variations in practice across Europe. Even where detailed studies have been undertaken, e.g., in the UK National Health Service [1995] where detailed information was collected on the weight of unused/ unwanted medicines taken back by 252 of the Primary Care Trusts (PCTs) data are incomplete and no information is available on the estimated relation between sold drugs, the rate of these drugs that are potentially unused, and the rate of unused drugs taken back to the pharmacy. In Germany, old unused medicines are legally classified as residual waste and can be disposed of with regular waste. Given the variable nature of the information collected across Europe, data sets from different countries are incomplete and incompatible, and efforts need to be made in this area.

Communication and good practices

Recommendation: Strategies to enhance public awareness of the impact of pharmaceuticals in the environment need to be developed in order to stimulate a more responsible approach to the use of medicines and their appropriate disposal.

Environmental hazards and risks of drugs should be emphasised in order to inform all actors of the life cycle of a drug of the potential environmental impact resulting from bad practices, use and/or management.

The knowledge on existing environmental data needs to be continually updated and continually converted into relevant and practical information. New information on the behaviour of drugs in the environment and on any effects on the environment should be presented in the same way as for new information on side effects and drug interactions, e.g. using the websites of relevant agencies.

Approaches to communicating methods of “good practice” to manufacturers, prescribers and users of pharmaceuticals can be proposed on the basis of current knowledge, particularly on acute and long-term effects. Strategies to enhance *public awareness* have to be developed in order to stimulate an environmental approach, and to allay unfounded fears. Society needs information and training regarding the effects of drugs on the environment in order to be able to make an informed, logical, objective assessment of risks. Currently there is generally a poor understanding of the concept of risk.

Information on pharmaceutical substances effects on the environment (when known) could be provided through products résumés and pack inserts, in a way that can be read and understood by the public. Moreover, package insert should contain instructions to return product to pharmacy. European legislation currently provides the opportunity for the product résumé to include information on veterinary drugs’ effect on the environment. An equivalent facility for human drugs would be relevant. This information has to be based on scientific data and not delivered in the form of an advertising message. FDA and EMEA make publicly available documents summarizing the environmental risk assessment for the approved submissions: these documents could be a means of capturing the technical data from the ERA.

In addition, more general information (brochures, posters) targeting the general public could provide directions on best practice in the disposal of unwanted or expired medicines, and how to return them. These brochures could be made available in pharmacies; their distribution could be extended to municipalities, and could be inserted in local newspapers, bulletins of healthcare communities (e.g., doctors and vets). Information should be disseminated as widely as possible through relevant websites and networks in order to encourage the public to embrace take back schemes. Short periodic awareness campaigns (for instance based on a simple scheme showing the routes by which unwanted medicines disposed of via the toilet or sink reach the environment) carried out through outlets for medication could be helpful in this context.

Increased awareness of students in primary and secondary education would be helpful since it has been observed that information about recycling, given at the primary school, influences the behaviour of parents. Hence this route provides an opportunity to achieve wider embracing of the environmental stewardship of pharmaceuticals.

The involvement of producers and distributors is also important. In addition to their involvement and their participation in take back schemes, they need to be more educated in the environmental considerations of the drugs. Universities could include environmental knowledge in courses for professional categories (doctors, pharmacists) involving prescription/handling of drugs. In the same way, information of the environmental effects of drugs could be introduced in environment related courses. The corresponding teaching aids (e.g. power points) could be made available on relevant websites of stakeholders (e.g., professional associations, environmental agencies).

Policy framework and instrument selection

Recommendation: The current policy framework is considered sufficient to deal with the issue of PPs in the water environment although implementation could be improved e.g. take back schemes. Environmental risk assessment procedures need to be kept up to date and should be applied to existing, as well as new medicines. The upgrading of wastewater treatment systems might be an option to reduce environmental residues further but it needs to be considered with respect to cost (both financial and environmental) risk and benefit.

The current policy framework is considered sufficient to deal with the issue of PPs in the water environment. No extra Directives are needed. In addition to the comprehensive framework provided by current guidelines of the ERA, the WFD provides an overall framework for the protection of water from pollution by chemicals in Europe. Nevertheless, the WFD management mechanisms & precautionary principle are not currently fully used for “PPs in water” due to the complexity, uncertainties and lack of knowledge on this issue. The initial WFD identification of pressures and impacts on water bodies (completed in 2005) has to be updated by 2013 and every 6 years thereafter. PPs can be incorporated into this scheme once more data have become available on their occurrence and ecological impacts in water bodies failing to reach the WFD objectives. Moreover, the ERA also has to continually improve its processes based on newest scientific findings. The position of “old medicines» still need to be addressed in the current ERA framework.

Where in several countries there are problems (partly related to lack of consumer awareness of scheme operation and of the general issue of PP in the environment) in the implementation of drug take-back schemes, these need to be addressed. Where drug take-back schemes are not yet present, there is an urgent need to establish them. The drafting of an EU guideline on take-back could be helpful.

Upgrading of wastewater treatment is another possibility in order to limit the occurrence of PPs in the environment. In this respect, economic instruments (e.g. sewage treatment fees) are one potential way to fund this option.

Finally, it is recommended that the selection of instruments for limiting discharges of PPs into water should be based on the following:

- New scientific knowledge on environmental risks & impacts of PPs;
- A balance between the appropriate level of scientific evidence on risk and the cost of measures;
- An assessment of the costs and benefits of optional instruments (e.g. benefits of take-back schemes for the environment; impact and effectiveness of environmental classification of PPs). Currently, the information available is not enough to permit a full assessment of all of the options. To assist decision-making on this issue, it is recommended that more information on costs and benefits be collected through targeted research projects and through pilot projects on the use of specific instruments;
- Until we have more targeted information, it is wise to recommend actions that will have broad benefit such as optimizing existing wastewater treatment that will improve the removal of many compounds or promoting return of unused drugs that also reduces the risk of unintentional poisonings.

4. Conclusion

Currently, Pharmaceutical Products do not appear to be a problem in terms of their environmental impact, but their presence is perceived to be an issue which represents a challenge for future management of the environment.

Moreover there is a consensus between the different actors involved in the PPs life cycle on the need to take action to limit their presence in the environment. Actions will depend on the level of the estimated risk. If the level of risk is considered very high, there is a need to act rapidly. But if the level of risk is uncertain (due mainly to lack of appropriate data) or considered as limited, there is no urgency to act.

The presence of human pharmaceutical products in the environment can be put down to their manufacture or their use in household and healthcare establishments. Currently the latter is by far the most important source.

In this deliverable, we consider the users of PPs as the key source responsible for the presence of these compounds in the environment and we propose some actions that can be take before, after or during the use of PPs. This is not an exhaustive list of recommendations but we try to highlight both the more relevant and the more achievable ones.

KNAPPE discussions have been valuable as a forum for an open and honest exchange of views by the stakeholders who have participated. Those who have taken part are committed to continuing the dialogue to seek to come to a better common understand of the issue and so to be better placed in the future to answer questions on this topic.

At this stage, ten recommendations have been selected on the basis of a collaborative work between the main actors of the PPs lifecycle, involved in Knappe project. They aim to fulfil two objectives:

Advance scientific and technical knowledge concerning fate and effect of PP's

- *Review effectiveness of current and potential removal STP processes*: the efficiency of wastewater and drinking water treatment processes need to be improved, either by optimising the existing systems or by the application of improved technologies.

- ***Increase knowledge of the environmental effects of PP's***: Further work is needed to establish the ecological relevance of sub-lethal responses, particularly the relevance of non-standard endpoints, the significance of metabolites and transformation products and to investigate how the impact of mixtures could be evaluated.
- ***Develop intelligent testing strategies for chronic toxicity assessment***: Intelligent testing strategies need to be developed to improve the assessment of chronic toxicity. This should include assessments of mode of action and utilise emerging data from 'omic' technologies
- ***Further investigate fate of PP's in STPs***: The interaction between PPs and solids, particularly in wastewater treatment plants needs further study. In particular, a better understanding of whether residues are permanently bound to solids or if they can be released back into the environment.
- ***Evaluate role of environmental monitoring in risk assessment***: There is a need to improve monitoring strategies. A priority list of PPs should be established, where possible spot sampling should be replaced by integrated methods and there should be a central repository for monitoring data using a standardised format.
- ***Evaluate practicalities of adopting a "green pharmacy"***: The development of 'greener' pharmaceuticals needs to be stimulated. This could be done by providing an incentive of increased patent life, or incorporating the outcome of the environmental risk assessment into the drug approval process.

Control of emission of PPs into the environment

- ***Evaluate effectiveness of classification schemes***: The Swedish system for the environmental classification of pharmaceuticals is a good method for providing information to health professionals and patients. We recommend that a general European framework for environmental classification should be developed which could be adapted from country to country in order to take into account the specificity in medical practices and the drug consumption of each country

- ***Unused medicines management:*** ‘Take Back’ schemes for unused medicines represent one of the simplest ways to reduce inputs of PPs to the environment. We recommend that quantitative information should be obtained on the efficiency of existing schemes and that each Member State should then seek to adopt best practice for such schemes, including the provision of information to patients. A European guideline could be very useful.
- ***Evaluate methodologies to better inform public:*** Strategies to enhance public awareness of the impact of pharmaceuticals in the environment need to be developed in order to stimulate a more responsible approach to the use of medicines and their appropriate disposal.
- ***Evaluate need for policy framework reform:*** The current policy framework is considered sufficient to deal with the issue of PPs in the water environment although implementation could be improved e.g. take back schemes. Environmental risk assessment procedures need to be kept up to date and should be applied to existing, as well as new medicines. The upgrading of wastewater treatment systems might be an option to reduce environmental residues further but it needs to be considered with respect to cost (both financial and environmental) risk and benefit.

These different actions have been developed in this report and show that all the stakeholders (manufacturers, healthcare community, patients, water managers and regulatory institutions) are involved in and committed to the reduction of PPs in the environment. It is important to note this, and to build on it. There is a need to extend this cooperative approach to include political decision makers in order to achieve an informed and sustainable management of pharmaceutical products.

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