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KNAPPE PROJECT

"Pharmaceuticals in the Environment" is an issue receiving growing attention. About 4000 medical compounds are being used in the drugs applied today. It is estimated that worldwide consumption of active compounds amounts to some 100 000 tons or more per year.

According to European guidelines, predicted environmental concentrations (PECs) of pharmaceutical products (PPs) in water must be equal to or more than 0.01 $\mu g.L^{-1}$ before further environmental risk assessment (ERA) is necessary. Some PPs and their metabolites are not removed from water during conventional biological treatment and enter the water supply via mainly urban wastewater treatment plants (WWTPs). These compounds can be biologically active, even at environmental concentrations (sub $ng.L^{-1}$ to $ng.L^{-1}$) and could, hence, be harmful to aquatic species. Their persistence is of particular importance, because it increases the risk of long-term exposure which could be responsible for chronic toxicity and subtle effects in animals and plants (endocrine disruption, growth inhibition, disruption of microbial ecosystems, cytotoxicity, mutagenicity, teratogenicity ...).

Spatial and temporal variations of the chemicals in water also make PEC determination difficult and uncertain. In recent years, research and studies on PPs in the environment have exponentially expanded; the research has, however, been fragmentary, dealing with only part of the problematic (occurrence, treatment, fate, or toxicity), resulting in a weak connection between the collected data and preventing from a holistic understanding of the issue of PPs in the environment as a whole. Therefore, there is a need to take into account the whole lifecycle of PPs (from manufacture to exposure) in order to improve environmental impact assessment.

A Specific Support Action (KNAPPE Project) was financed by the European DG Research (in a frame of the 6FP) to make the state of the art of the current knowledge in this topic in order to identify the main gaps and answer several questions deserving attention such as:

- What is the list of most relevant PPs in terms of exposure for the aquatic environment? Which indicators for supporting environmental managers, health authorities?
- What is the efficiency of urban and industrial sewage treatment plants over a year? What is the fate and behaviour of PPs in sewage treatment plants? If receiving waters are used for potable water supplies, does the presence of these compounds represent a potential hazard to human health?
- Could we solve some problems by environmental or cleaner technologies?

- What regulatory approaches, incentives, prevention actions can be implemented in order to lower PPs concentration in the environment? Does a European practical guidance can be developed?
- Can the environ mental impacts of PPs be reduced through the use of eco-pharmacostewardship approaches including the use of clean synthesis, classification and labelling, and better communication of methods of 'good practices'?
- How can we better monitor the environmental impact of a drug once it has received a marketing authorisation?
- How can we manage the discharge of PPs in the environment?.

KNAPPE project has initiated discussions through workshops and conferences with the concerned groups of experts (pharmaceutical industry, water managers, healthcare community, patients, regulatory institutions) and provide the information to all stakeholders by means of the maximum readable ways.

Overview of KNAPPE objectives

Decision No. 2455/2001/EC in accordance with the WFD established a list of "priority substances selected from amongst those that present a significant risk to, or via, the aquatic environment". This list is based on the toxicity, persistence, bioaccumulation potential, human health risk and the monitored and modelled concentration of each substance in the aquatic environment. Some other substances (emerging pollutants) identified by the United States Geological Survey (USGS), can be considered as a complementary list likely to be of relevance to the WFD in the future[1]. The ecological and human health impact of emerging pollutants in water and more particularly in wastewater effluent has in recent years come to the attention of scientists as well as environmental regulators. The United States Geological Survey (USGS) has identified 95 emerging pollutants of concern. Many of these compounds may be found at low concentrations in treated wastewater and sometimes in potable water. Although this is a relatively novel area of research, there are some concerns that exposure to emerging pollutants may cause cancer as well as physiological changes in humans and animals. Of particular concern, is human and animal exposure to so-called Pharmaceutical and Personal Care Products (PPCPs). These compounds, coined by Daughton and Ternes[2], are described as a very broad, diverse collection of thousands of chemical substances, including prescription and over-the-counter therapeutic drugs, fragrances, cosmetics, sun-screen agents, diagnostic agents, neutraceuticals, biopharmaceuticals, and many others. This broad collection of substances refers, in general, to any product consumed by individuals for personal health or cosmetic reasons.

PPs are mainly excreted in urine or faeces. Hence, they enter municipal sewage treatment systems where they can be degraded, adsorbed in the sewage sludge, or eventually diluted into surface water. At this stage, PPs which are not removed end up in the aquatic environment. Adsorbed compounds can reach the terrestrial environment when sludge is used as an agricultural fertilizer. Agricultural land can also be exposed when manure from medicated in house reared animals is spread. Pharmaceuticals used in animals raised on pastures are excreted directly to the grassland. Pharmaceuticals entering the terrestrial environment can reach surface water and

[1] D. W. Kolpin, E. T. Furlong, M. T. Meyer, E. M. Thurman, S. D. Zaugg, L. B. Barber, H. T. Buxton, 2002, Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance? Environ. Sci. Technol. 36, 1202.
[2] C. G. Daughton, T. A. Ternes, 1999, "Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change?" Environ. Health Perspect., 107(suppl 6), 907-938

groundwater. In addition, pharmaceuticals used in aquaculture are released directly into surface water. Figure 1 shows the different pathways of pharmaceuticals to reach environmental compartments. Yellow boxes represent the different actors of the life cycle of the medicine (from the manufacturer to the water distributor), and the blue ones, the main environmental compartments of concern.

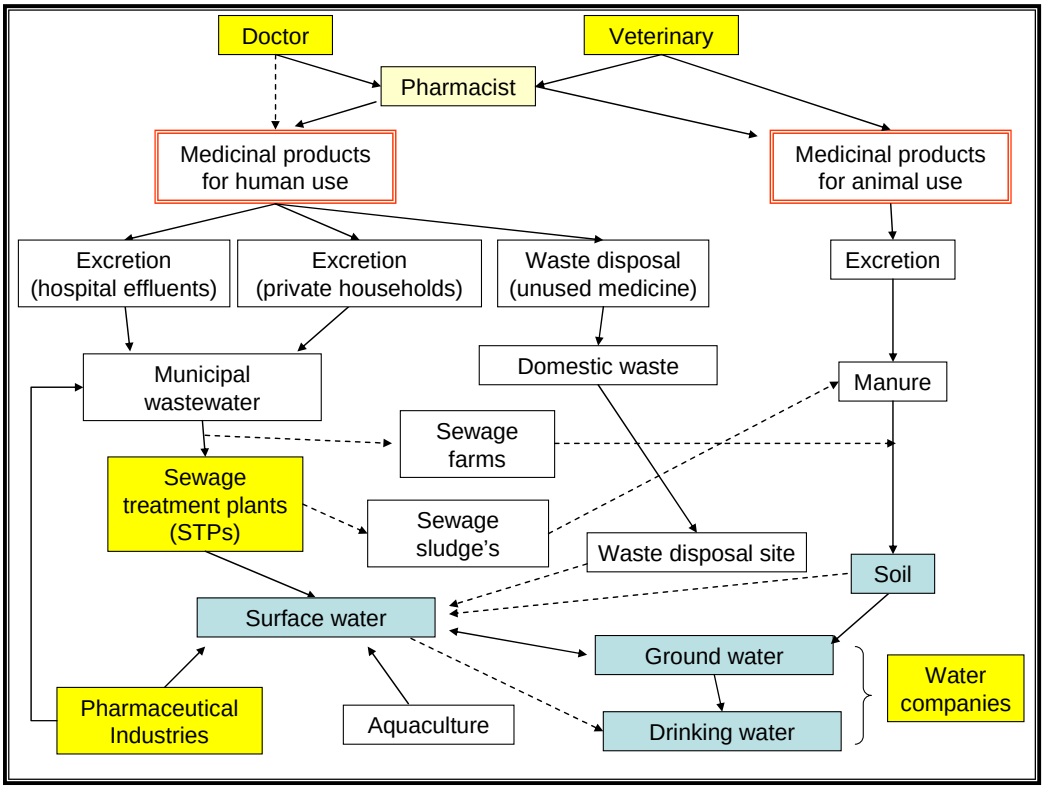


Figure 1: Medicine Environmental Life Cycle

Before a PP can be marketed in the EC, it is necessary for companies to perform an environmental risk assessment (i.e. Directive 2001/82/EC for veterinary medicines and Directive 2001/83/EC for human medicines). Typically, these assessments involve the generation of data on the environmental exposure and ecotoxicity of PPs. In selected instances, risk management approaches may need to be developed and assessed during the registration process. Following authorisation, regulators and industry in member states are typically required to monitor the in-use safety of a PP using pharmacovigilance schemes. Increasingly, pharmacovigilance approaches are considering environmental endpoints (eco-pharmacovigilance[3]).

[3] Eco-pharmacovigilance is a sub discipline of pharmacovigilance. The term is increasingly being used (e.g. it was a topic of discussion at a recent Pellston workshop on veterinary medicines in the environment) to describe chemical and biological methods that can be applied following marketing authorisation to monitor effects on environmental health.

Three EU projects, ERAVMIS, REMPHARMAWATER and POSEIDON, in the 5th Framework have studied the behaviour and impact of human and veterinary PPs in the environment, as well as the most effective water treatment processes to eliminate these compounds from both waste-water and drinking water. The above studies provided the first data to enable the assessment of the presence and effects of PPs in the aquatic environment and soils at the European level. They also proposed solutions to the problem of the removal of PPs from waste water (e.g. by advanced oxidation techniques or by sunlight). Furthermore, they have demonstrated that microbial populations appear to change due to exposure to antibiotics. An increase in antibiotic resistance has been seen around the world, making treatment of some diseases difficult. In the 6th Framework Programme, two other EU research projects (ERAPharm, EMCO) have been focussed respectively on the improvement of knowledge and procedures for the assessment of environmental risk due to human and veterinary pharmaceuticals, and on tracing emerging contaminants in industrial and municipal wastewaters and their removal by advanced water treatment technologies. Other programmes, NORMAN and PTHREE, have concerned more generally with a wide range of emerging pollutants and are focussed on analysis and treatment respectively. Apart from these EU funded research projects, progress has been limited and therefore, it is important to increase our knowledge of these compounds, their behaviour and impact on the environment in order to better protect aquatic environment from contamination and develop prevention strategies.

It is clear that PPs should be considered as an environmental concern and consequently will require priority actions in the near future. It is therefore essential to identify the real priorities to be addressed in order to increase the effectiveness of research at the European scale.

In this context, KNAPPE project proposes to carry out a review of the state of knowledge and put emphasis on questions deserving attention by pulling together results of previous and on going EU projects and published data from both governmental sources and scientific literature, by involving manufacturers in supplying data on production and use of pharmaceuticals. These topics of concerns include occurrence, detection, fate, behaviour, removal treatments, known environmental and health impacts of these molecules and stewardship approaches. On the basis of these data, the final objective of the project is to identify the relevant priority actions to be taken in the framework of a sustainable development, more especially in terms of lowering presence, impacts and risk of PPs in the environment. In particular:

1 – KNAPPE will help to establish a potential "traceability" of PPs in the aquatic environment and elaborate indicators supporting water managers, health authorities and persons involved in river basin management plans and strategies to minimize discharge of PPs in the environment,

2 – KNAPPE will investigate the elimination efficiency of treatment processes (sewage treatment, drinking water production, specific industrial processes). The project will suggest different strategies for PPs treatment with identification of necessary enhanced for future requirements (suggestions for treatment at the source, or restrictions of use) and assessment of cost effective adaptations (or modification) to current treatment plants,

3 – KNAPPE will present an overview of the eco-toxicological significance and health impacts of PPs and identify needs for developing complementary data/approaches to prioritise PPs (chemical by chemical, class by class or mode of action basis),

4 – KNAPPE will assess regulatory approaches at European level and existing legislation and instrument on the discharge of PPs and carry out a gap assessment. KNAPPE will develop cornerstones for supporting the aims of WFD by highlighting opportunities arising from various instruments and measures for a European prevention action,

5 – KNAPPE will propose recommendations for environmental stewardship (pollution prevention and monitoring) integrating green technology and vigilance scheme and develop a document dedicated to all stakeholders,

6 - KNAPPE will hold several international events (stakeholders workshops, scientific conferences) involving regulators, scientists, doctors, industry … in which discussions and exchange will take place.

7 – KNAPPE will disseminate its recommendations and main findings throughout Europe, notably by making them available to the public on a web site and by publishing them in scientific journals as well as by giving presentations to the scientific community and decision makers. A CD Rom compiling all the results will be generated and distributed the most widely as possible.

KNAPPE methodology

To reach these objectives, KNAPPE project has considered the whole life cycle of PPs and tried to interconnect data of each steps.
KNAPPE proposed an integrated approach (Figure 2) from the manufacture to the environmental exposure by collecting data and information, pulling together them and presenting them to the different actors (through meetings, workshops, conferences) involved in the life cycle in order to promote discussion and exchange.

Available data and information have been collected through 5 technical workpackages (WP):

- WP1 (***Occurrence of PPs in the aquatic environment: towards indicators for contamination with pharmaceuticals***) the objective of which was (i) to establish a list of PPs most relevant in terms of exposure for the aquatic environment, (ii) to identify the major gaps in terms of data availability and data quality and (iii) to propose environmental PPs indicators to elucidate the contamination source.

- WP2 (***Assessment of limits of the current water treatment processes: towards best practices for lowering PPs contamination in the aquatic environment***) the objective of which was to put emphasis the causes and effects of deficient wastewater treatment efficiencies and open the discussion of the future evolution to limit them.

- WP3 ***(Develop cornerstones of an EU prevention action to limit the discharge of PP into aquatic environment***), the aims of which were to (i) gather relevant information concerning existing regulations in EU dealing with the discharge of pharmaceutical products into water, (ii) evaluate the options arising from different instruments (e.g. regulatory approaches, incentives) to limit the discharge of pharmaceutical products into water, and (iii) highlight opportunities arising from various instruments and measures such as taxes, voluntary approaches, regulations, co-operations to protect waters from such pollutants.

- WP4 (***Health and environmental impacts/effects related to PPs***) that (i) reviewed the data on the effects of PPs on aquatic and terrestrial organisms and humans (ii) explored the

significance of the reported effects in terms of environmental and human health, and (iii) furthered the understanding of the impacts of PP transformation products and mixtures of PPs on ecosystem functioning and human health.

- WP5 (***Eco-Pharmacostewardship and vigilance***) the objectives of which were to (i) review the role of eco-pharmacostewardship and vigilance throughout the lifecycle of PPs, (ii) further understanding of how and where stewardship and vigilance schemes can be adopted to improve the overall sustainability of PPs and (iii) identify existing examples of good practice, study drivers for increased uptake and develop strategies for increased development of greener drugs

In addition to these technical works, a workpackage (WP6) dedicated to communication, dissemination and proposition of recommendation for reducing PPs in the environment has been implemented.

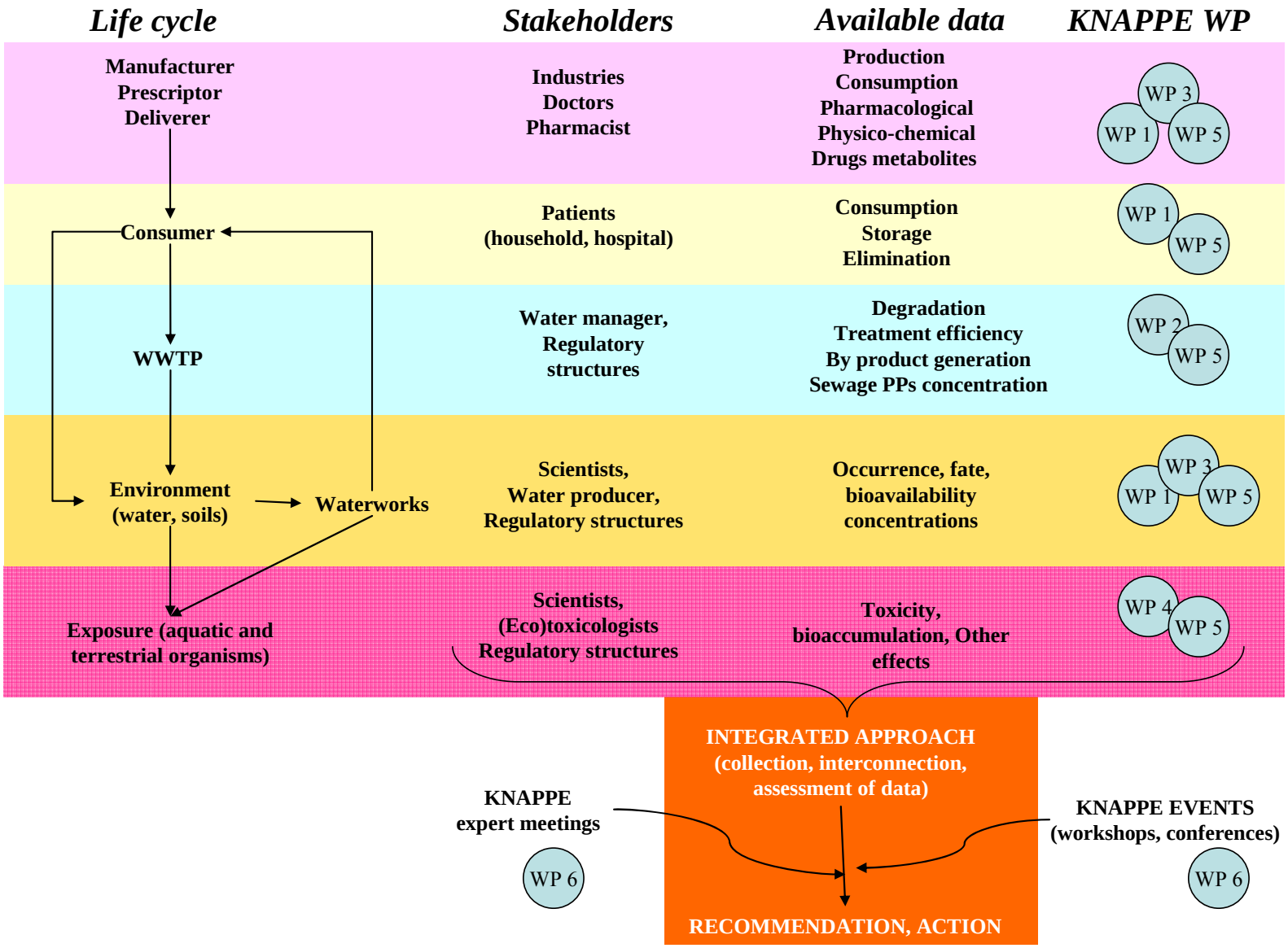


Figure 2: KNAPPE methodology

Work packages results have been presented and discussed during the Executive Committee (EC KNAPPE expert meetings). This working group was made up of KNAPPE WP leaders and some external experts including the major stakeholders of concern (Table 1).

Table 1: Members of KNAPPE Executive Committee

Stakeholder nature	Structure participating to Executive Committee
Human Pharmaceutical Industry	European Federation of Pharmaceutical Industries and Association (EFPIA), Association of British Pharmaceutical Industries (ABPI), AstraZeneca, Sanofi-Aventis, MSD, Janssen Pharmaceutical
Veterinary Pharmaceutical Industry	International Federation of Animal Healthcare (IFAH)
Scientific organisations	Society of Chemical Industry (SCI), SETAC (Society of Environmental Toxicology and Chemistry), GCN (Green Chemistry Network), Norman (Network of analytical laboratories)
Consumers organisations	European Patients' Forum, C2DS (French Community of healthcare actors involved in Sustainable Development)
Water companies	SAUR, Suez-Environment
Sanitary agencies	French Agency For Food Sanitary Safety (AFSSA), French Agency for Sanitary Safety in Health Products (Afssaps)
Research institutes	INERIS, BRGM, BfG, EMA, CEMAGREF, Univ. Freiburg, IVL

The role of the EC was to check the KNAPPE programme strategy and evolution, to outline expectations from stakeholders, to promote discussions and exploration of new ideas and to participate actively to KNAPPE events. The implementation of the EC was a major step because it allows to promote the project and to make credible the real expectations of stakeholders involved in this problematic.

On the other hand, to open the project findings to a wider audience, four workshops were organised involving regulators, scientists, doctors, industry … in which discussions and

exchanges have taken place. These workshops have been leaned against the different work packages, addressing the following issues:

- WS1: Occurrence of PPs in the environment: PPs owe their origins to their universal, frequent and highly dispersed but cumulative usage by lots of individuals. What are the full extent, magnitude and ramifications of their presence in the aquatic environment?

- WS2: Toxicological significance of PPs: On the basis of present knowledge, are available data sufficient for assessing fate and effects of PPs in the environment and health impacts? What are the potential for subtle long term effects (effect on growth, ability to reproduce), the risks of mixtures (additive/interactive/cumulative exposures and effects)?

- WS3: Regulatory instrument design to limit pollution from PPs: This workshop has discussed preliminary results on proposition of future instrument and measures that will limit discharges of PPs

- WS4: Environmental stewardship of PPs: This workshop has explored ways in which the impact of a PP on the environment can be reduced at all stages of the PPs life cycle (production, prescription, use and disposal).

Finally, in complement to these workshops, the discussion and presentation of which have been based on available knowledge, an International Conference, investigating new trends for lowering the presence and the impact of PPs in the environment and based on future development or on going studies has been organised.

A total of around 30 deliverables have been produced gathering the results of these investigations.

Main achievements related to current knowledge

- WP1 : ***Occurrence of PPs in the aquatic environment: towards indicators for contamination with pharmaceuticals***

An extensive data compilation on the environmental occurrence of PPs was created, including 58400 measurements of 178 pharmaceutical products in 22 countries in WWTP influent, WWTP effluent, surface water, groundwater, bank filtrate, marine water and drinking water. For each country, average mean environmental concentrations (A-MECs) were calculated from the compiled data for each PP, regarding the seven aquatic matrices, when measurements were available. Additionally, consumption data of PPs for five European countries (France, Germany, Poland, Spain and the UK) have been used to predict their environmental concentrations following the approach used in the EU-Project Poseidon.
A comparison revealed that predicted and averaged measured environmental concentrations matched well for WWTP influent. For WWTP effluent and surface water, the agreement of the data was limited to some extent, as consumption data was frequently lacking the PPs used in freely available OTC-products. Furthermore, transformation processes in surface waters were not covered by the prediction model.

The data compilation was used to establish a set of indicator substances for the determination of the wastewater share in surface waters and for determining whether a water body is influenced by poorly or raw wastewater.
Indicator substances for the determination of the wastewater share are:

- Diatrizoate (iodinated X-ray contrast medium)
- Iopamidol (iodinated X-ray contrast medium)
- Carbamazepine (antiepileptic)
- Erythromycin (antibiotic)
- Metoprolol (betablocker)

Surface waters contaminated with these compounds are expected to contain a variety of other polar persistent organic compounds, which were also not removed during wastewater treatment.

Indicator substances showing the presence of non- or poorly treated wastewater are:

- Ibuprofen (analgesic)
- Paracetamol (analgesic)
- Salicylic acid (analgesic)
- Bezafibrate (lipid regulator)

The presence of these indicator substances which are readily (bio)degradable in wastewater treatment, in surface waters indicate the input of non or poorly treated wastewater with potential consequences for water quality and water usage, concerning pollutants and pathogens.

No PPs could be classified as indicator substances specific for the input from hospitals or veterinary medicine. Potential indicator substances for hospital input either lacked the specificity of only being used and excreted in a hospital environment or their environmental concentrations were too low for a reliable quantification.
Due to the different registration situation in the various countries, with deviating and/or overlapping use in human and veterinary medicine, no pharmaceutical compounds are in general fully attributable to veterinary purposes only.

Indicator substances expected to be present in groundwater which influenced by wastewater are the following, all being relatively polar and persistent:

- Diatrizoate (iodinated X-ray contrast medium)
- Iopamidol (iodinated X-ray contrast medium)
- Carbamazepine (antiepileptic)
- Sulfamethoxazole (antibiotic)

Currently, the available data on the consumption and the occurrence of PPs in the aquatic environment on a European level is of very limited comparability. Efforts should be made to achieve a common book keeping system on the usage of all pharmaceutical products within the EU, including prescribed PPs, OTC drugs, and all compounds used for diagnosis and in hospitals.

The available environmental exposure data on PPs is very limited in quantity, concerning the diversity of PPs, their metabolites and environmental transformation products, the number of

available measurements in the different aquatic/marine compartments being measured and concerning data quality, sampling, analysis and data evaluation.

Future monitoring studies should close the existing data gaps in the current knowledge and overcome the challenge of data comparability.

- WP2: ***Assessment of limits of the current water treatment processes: towards best practices for lowering PPs contamination in the aquatic environment***

The works performed in this WP allowed to assess the efficiency of elimination of PPs by conventional treatment processes and to identify new treatment processes under development.

In a first time, a comparison of the wastewater and drinking water treatment technologies in regard to PPs removal has been made. Data concerning pharmaceutical compounds removal was collected and set in following order:

- Sewage treatment plant (STP) characteristics;
- Removal.

Then, in order to highlight the differences of the crucial parameters impact on the elimination of PPs, literature data was described according to the following factors:

- Sludge retention time (SRT),
- Hydraulic retention time (HRT),
- Reactor configuration,
- Red-ox conditions,
- Climatic zones
- Advanced technologies.

In case of drinking water, the data regarding variety of treatment technologies was collected and, likewise in case of wastewater treatment, set in following order:

- Process description;
- Removal.

All pharmaceutical compounds found in the available literature data were divided into therapeutic groups: antibiotics, anticonvulsants, antiinflammatories (analgesic), β-blockers, hormones, tranquilizers, X-ray contrast media and lipid regulators.

According to the available data concerning wastewater treatment it can be stated, that sewage treatment plant (STP) (e.g. conventional activated sludge processes, membrane assisted bioreactors) configuration is not a factor, which have the highest impact on the PPs removal. It is rather connected with parameters, such as sludge retention time (SRT) and hydraulic retention time (HRT) which seem to be the crucial parameters and the visible correlation with the PPs removal rates can be observed.

Such correlation was not found for the climatic zones, however consumption pattern of PPs in each country or region could have significant impact on the chosen compounds elimination.

In regard to drinking water, it can be concluded that the ozonation was the most efficient treatment technology for the majority of compounds. However, the efficiency depends on the reagent dose and combination with other oxidants, pH and presence of OH radical's scavengers.

In a second time, strategies for minimize the PPs discharge to the environmental waters have been investigated by evaluating the following issues:

- *Identification of groups of human pharmaceuticals according to their removal rates by current biological sewage treatments and try to establish links with their physico-chemical properties.* The PPs belonging to the same therapeutic groups do not show the similar removal. It is caused by the fact, that they possess a different chemical structure and/or differ in issue/organs action. Moreover, similar skeleton groups bound with the similar functional group results in similar biodegradability. On the other hand, biodegradation of the strong hydrophobic compounds are usually not very high, the removal of such substances are due to sorption on the sludge particles.

- *Assessment of concentrations of pharmaceuticals in sewage sludge and hence their potential contribution to the pollution of environment for sludge reuse or disposal.* There exists an information gap concerning PPs concentration in sewage sludges. Available literature shows no data on behaviour of the PPs during the sewage sludge treatment (preliminary

treatment (screening, comminuting), primary thickening (gravity, flotation, drainage, belt press, centrifuges), liquid sludge stabilization (anaerobic digestion, aerobic digestion, lime addition), etc.). However, it is commonly known, that sorption is one of the significant processes in PPs removal mechanisms and directly link with the treatment of the sewage sludge. A sorption or distribution coefficient (Kd) is commonly used to describe this process and it is distinguished for primary sludge and secondary sludge. The Kd value allows, in some extent, to predict the sorption behaviour in Wastewater Treatment Plants. According to the literature data, for compounds showing the sorption coefficient below 500 L/kgSS onto primary sludge and 300 L/kgSS onto secondary sludge can be negligible. In case of the sludge treatment processes, the limit of the relevance of the sorption coefficient is around 1 L/kgSS, because of the much higher concentration of the sludge. Taking into consideration, that there are single records concerning sorption and desorption processes of many PPs and that landfilling is the most common strategy for sludge disposal (35 – 45%), it can be concluded, that there is strong need for further investigation concerning behaviour PPs during treatment of sludges.

- *Possibilities to improve the existing technologies*. According to the available data, the current municipal STPs are not able to guarantee a complete elimination of PPs. However, there are some possibilities of the enhancing PPs removal at the existing facilities:
  - the optimum SRT range within 10 – 20 days,
  - the optimum range of HRT for PPs elimination varies from 12 to 25 hours.

Additionally, the pre or post treatment in some cases is effective, e.g. reverse osmosis, however, removed pollutants are concentrated in the waste stream, which also must be treated itself; the treatment by means of AOPs can lead to creation toxic by-products.

- *Suggestion of different strategies for PP treatment with identification of future requirements (suggestions for treatment at the source, even restrictions in use)*. Source control and source separation could be implemented in order to reduce or minimize the introduction of pharmaceutical compounds to the environment (i) if the treatment before the dilution in the sewage system is more effective, or (ii) if the losses during the transport via sewer system are to be avoided.

A wide range of protective actions could be implemented in order to reduce or minimize the introduction of pharmaceutical compounds to the environment (for example classification of pharmaceuticals, targeted therapy instead of prophylactic or empiric consumption of medicine). Furthermore, the source separation implemented for domestic or hospital wastewater, aimed to

elimination of PPs, would also reduce the concentration of pharmaceuticals in influents to the WWTPs. These actions would have an impact on the performance of the WWTP, because of the minimizing of the PPs load in the raw wastewater, what could be crucial point in the face of new regulation. The project, concerning environmental quality standards in the field of water policy, was presented in March 2007 and includes some PPs (Amidotrizoate, Diatrizoate, Carbamazepine, Diclofenac, Iopamidol) among the priority substances.

- WP3: ***Develop cornerstones of an EU prevention action to limit the discharge of PP into aquatic environment***

This WP reviewed key existing policy instruments and approaches at EU level and in selected Member States, which are relevant to limiting the discharge of pharmaceutical products into the water environment. Policies treated in this state of the art addressed issues of authorisation of PPs, pollution prevention, wastewater treatment as well as monitoring of environmental quality.
The review paid attention to regulations directly relevant to human medicinal products but also to broader environmental protection policy. The analysis has served as a basis for the identification of possible gaps in current approaches.

At the European level, ***regulations on pharmaceutical products*** and on the environmental risk assessment in their authorisation process are quite recent: Directive 2004/27/EC on human medicine, Directive 2004/28/EC on veterinary medicine. Although separate regulations exist for "human medicinal products" and "veterinary medicinal products", these two categories of PPs are addressed in consecutive regulations which are based on the same principles and are highly similar in content. According to Directive 2004/27/EC on human PPs, for all new authorisations of PPs, the environmental effects must be examined and this assessment must accompany the authorisation application. The environmental risk assessment typically involves the generation of data on the environmental exposure and ecotoxicity of PPs. Prior to 2004, detailed environmental risk assessment was only carried out in exceptional cases for human medicine. However, the granting of a marketing authorisation of human medicine cannot be refused using the environmental impact as criterion.
For veterinary PPs, the situation is different. Contrary to human PPs, the granting of a marketing authorisation of a veterinary medicine can be denied due to an unacceptable risk for the environment. The 2004 EU regulatory amendments indeed introduced certain key changes in the

authorisation of veterinary medicines. The criterion of environmental safety has been given the same weight as consumer safety in the concluding risk-benefit assessment and, therefore, can decide about the authorisation or non-authorisation of a new veterinary PP.

Currently, the environmental risk assessment (ERA) of human pharmaceuticals is based on the Guidelines of the European Agency for the Evaluation of Medicinal Products (EMEA) and the environmental impact assessment (EIA) of veterinary pharmaceuticals is based on the VICH guidance (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products).

On the other hand, in EU medicinal legislation, there are provisions to set up take-back schemes for unused and expired medicine in all Member States. Such take-back schemes are required by EU legislation since 2004. Directive 2004/27/EC requires Member States to "ensure that appropriate collection systems are in place for human medicinal products that are unused or have expired" (Article 127b). Reference to these collection systems is to be made on the labelling or package leaflet.

Concerning, the main ***Environmental protection regulations and policies*** such as Water Framework Directive (2000/60/EC), Drinking water Directive (98/83/EC), Bathing Water directive (2006/7/EC), Groundwater Directive (2006/118/EC) or Urban Waste Water Treatment Directive (UWWTD) (91/271/EEC, amended by Directive 98/15/EC and EC Regulation 1882/2003), no pharmaceutical products are included on the list of substances of particular interest to control and monitor. The main reason for this can be seen in the selection process for the first list of priority substances, which dates back almost 10 years and was based on already existing official lists of pollutants. PPs, however, are often referred to as emerging pollutants, which means that their presence in and impact on the aquatic environment is just being discovered and researched.

In other EU policies or initiatives: *European Strategy for Soil Protection*, Sewage Sludge Directive (Directive 86/278/EEC, amended by Directive 91/692/EEC and EC Regulation 807/2003), *Endocrine Strategy,* REACH Regulation *(*No. 1907/2006), *IPPC Directive*, although pharmaceutical substances are not part of the current EU policy documents, they have been identified as a priority issue for further research.

On the other hand, despite our limited current understanding of the emerging issue of PP occurrence in the water environment and only few cases of confirmed environmental impacts of PPs, the scientific community tends to agree that, for the sake of the precautionary principle, we should explore **ways to limit the input of PPs into the environment**, thus anticipating action needed in the future. Indeed, there is no clear picture yet within the pharmaceutical industry of the potential PP risks for the environment but it cannot be denied that there might be risks unknown at present.

All in all, the future selection of instruments that should be applied for limiting PP discharge 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 management strategies and instruments.
- 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 schemes of PPs).

Currently, information available is not enough for a full assessment of all options. To assist decision-making on this issue, more information should be collected and evaluated on the costs & benefits via targeted research projects as well as pilot projects on specific instruments.

Until more targeted information on PP occurrence and impacts as well as on instrument effectiveness and costs is available, it is wise to recommend actions that have broader benefits. For instance, optimizing existing wastewater treatment can improve the removal of many compounds other than PPs from wastewater and promoting drug take-back schemes can also reduce the risk of unintentional poisonings.

In a survey of expert stakeholders' views (based on 27 interviews) which included government, academia, pharmaceutical and consulting industries, it was suggested that a mixture of strategies addressing the various stages of the life cycles of PPs should be used in management (Doerr-MacEwen & Haight, 2006).

Within the KNAPPE project, the following instruments have been discussed and proposed as good management practice for preventing and limiting PP discharge into water:

- *Upgrading of wastewater treatment*, which is a cost-intensive strategy but could be financed via economic instruments, e.g. sewage fees or taxes. The upgrading of wastewater treatment can have a direct impact on the improvement of environmental quality as well as synergies with other environmental issues, especially the removal of other micro-pollutants from wastewater.
- *Wastewater collection & treatment at hospitals.* There are several projects testing this alternative, e.g. in the Netherlands and Germany, showing that this is seen in some countries as both a significant and viable approach.

- *Set up and/or improvement of the operation of drug take-back schemes.* Drug take-back schemes is one of the less cost-intensive management strategies accompanied by positive synergies with public safety (e.g. from accidental drug poisoning) and increased public awareness on the issue of PP occurrence in the environment. It is recommended that the drafting of an EU guideline on take-back schemes could be helpful to further establish this management strategy in European countries.

- *Improving the implementation of the current policy framework.* The current policy framework is considered sufficient to deal with the issue of PPs in the water environment. No extra Directives are needed. Next to the quite complete framework provided by current guidelines for ERA, the WFD provides an overall framework for water protection from chemicals in Europe. Nevertheless, certain implementation gaps exist and, in order to close them, we need a better understanding, data & research on PPs in the water environment.

Recommendations to improve the current policy framework include improving ERA data quality & accessibility, continually improving ERA on the basis of newest scientific evidence, addressing the issue of "old medicine" in the ERA framework, e.g. by testing representatives of non-tested PP classes, as well as addressing PPs in the framework of the Water Framework Directive (WFD) implementation. PPs can be incorporated more consistently into the WFD scheme of identifying water pressures and impacts, once more data have become available on PP occurrence and ecological impacts in water bodies failing to reach the WFD objectives.

- *Environmental classification of PPs for communicating risk to doctors and public.* This strategy is being explored for possible application in other European countries beyond Sweden. The actual effectiveness of the scheme in practice is subject of ongoing research.

- *Good prescription practices for a wiser use of PPs and limiting over prescription*
- *Economic instruments* based on the polluter-pays-principle (e.g. sewage treatment fees to fund the upgrading of wastewater treatment) as well as economic incentives for the production/consumption of "greener" PPs.

Some additional instruments were also raised but these need to be further discussed with stakeholders and assessed before considering them for possible application: Partnerships between UWWTP operators & prescribers (doctors, pharmacists) in their catchment; the consideration of environmental risk criteria in hospital procurement; and, finally, the use of ecolabels for PPs (mainly OTC drugs).

- WP4: ***Health and environmental impacts/effects related to PPs***

Medicines play an important role in the treatment and prevention of disease in humans and animals. During their manufacture and use, they may be released to the environment by a number of routes. Even though the side effects on human and animal health have been widely documented, only recently have the potential environmental impacts of the manufacture and use of medicines been considered. The data review showed that there is now a large body of data that has been generated over the past decade on the effects of pharmaceuticals on aquatic organisms. Using this data, generally, pharmaceuticals show low acute toxicity to fish, daphnids and algae and while the majority of pharmaceuticals also show low toxicity in standard chronic studies, a number of pharmaceuticals are highly toxic in standard chronic tests. A comparison of standard acute and chronic test endpoints with available monitoring data indicate that, with a few exceptions, pharmaceuticals do not pose an unacceptable risk to the environment. The effects of a number of pharmaceuticals have also been assessed using non-traditional ecotoxicity tests and endpoints. The effect endpoints for the majority of these novel tests are many orders of magnitude lower than the traditional endpoints and existing uncertainty factors do not reflect these differences. Additionally, most of the novel endpoints can be linked to important ecological functions so can be regarded as ecologically relevant. However, even when novel data are included in the risk characterisation, most pharmaceuticals seem to pose a low risk to ecosystem health. There are however some exceptions that may need further assessment or control in the

future. Some key findings have been discussed during the workshop 2 and further works have been identified as mentioned in P15.

On the other hand, prioritization of human pharmaceuticals is necessary due to the high number of pharmaceuticals used, which hinders the possibility to assess the ecotoxicity of every compound. To implement a relevant prioritization strategy, there is a need to accurately assess the environmental exposure and the environmental effects. From the review of ERAs and prioritization strategies conducted in the last ten years, it is possible to highlight the following parameters and to propose some concluding remarks:

Regarding exposure assessment:

- The use of simple models, as EMEA model, to calculate PECs for surface water is in general in good agreement with field measurements.
- Accurate, consumption amounts are essential, but data are sometimes unavailable, depending on the country.
- Metabolism data and excretion rates are essential but data are often incomplete or unavailable.
- STP removal rates are lacking which is a major limitation of the accuracy of ERA.
- PEC for other compartments than water column is not well assessed.
- Bioaccumulation of pharmaceuticals remains to be more studied.

Regarding effect assessment:

- Chronic ecotoxicological data are lacking.
- Due to gaps in ecotoxicological data for pharmaceuticals (due to the high number of pharmaceuticals), other ways of assessing the effects of pharmaceuticals have to be investigated and validated.
- Pharmacological data can be useful to estimate the biological effects on aquatic organisms however, i) the access to such data is sometimes not possible, ii) the relevance of such data for environmental considerations remains to be confirmed.
- Investigation of the evolutionary conservation of drug targets is important information that can help for a relevant use of pharmacological data, and for targeting sensitive species in bioassays.

- QSAR models should be investigated with regard to pharmaceuticals, which are compounds with specific mechanisms of action.

Thus, it becomes necessary to harmonize the different prioritisation strategies and models now available in European countries. As pharmacological and toxicological data are not easily available, the ERA of old pharmaceuticals at least, could greatly benefit from the development of a database on existing pharmacological and ecotoxicological data.

- WP5: ***Eco-Pharmacostewardship and vigilance***

First challenge of this WP was to show if the impacts of Pharmaceutical Products (PPs) on the environment could be reduced through the use of eco-pharmacostewardship approaches including the use of clean synthesis, classification and labelling and better communication of methods of good Practice.
Figure 3 summarizes the eco-pharmacostewardship approaches and opportunities that have been identified which could be applied to reduce the impact of PPs on the environment at all stages in the lifecycle. All of these factors should be taken into consideration when developing new PPs to ensure that they have as few adverse effects as possible whilst at the same time maximising their beneficial effects, leading to the development of a new generation of green and sustainable pharmaceutical products.

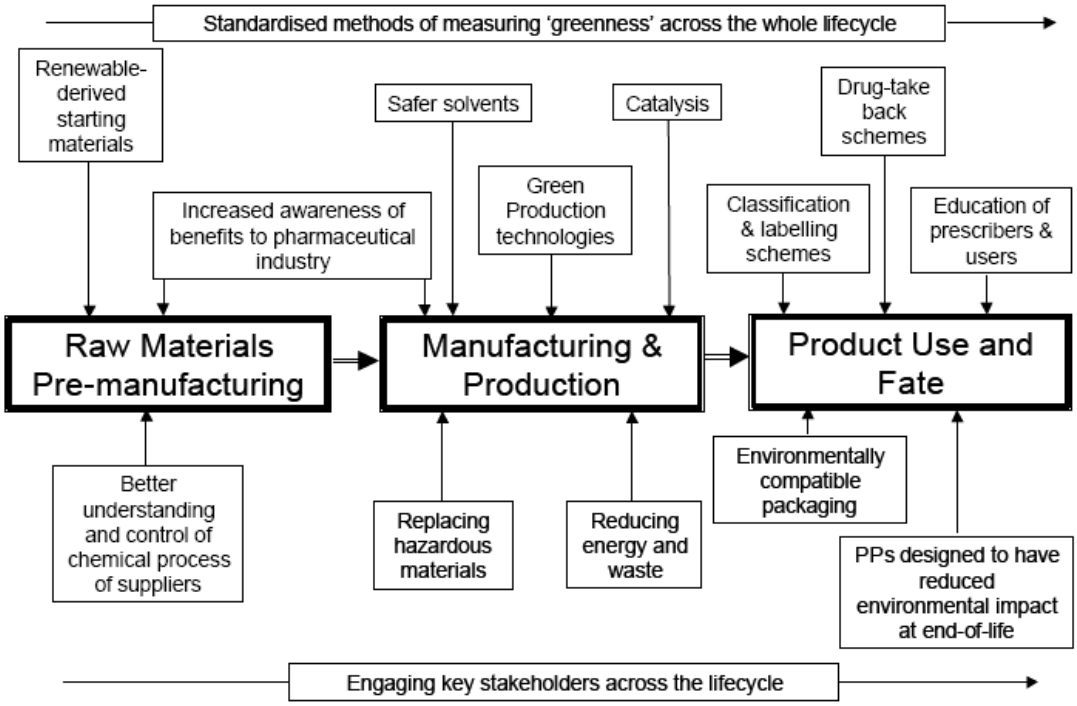


Figure 3: Ecopharmacostewardship approaches & opportunities to develop new generation of green and sustainable pharmaceutical products

During the project, some ideas have been proposed and discussed for the increased Development of Greener PPs such as for example:

- The implementation of tax or other incentives to make benign-by-design clean synthesis methods, green production technology and other stewardship approaches more attractive. Encourage pharmaceutical companies to make increased use of renewable resources part of company longer-term (e.g. 5+ years) plan (possibly extending to renewable energy). This should be done alongside a campaign to increase awareness of the benefits of increased uptake of these methods (e.g. reduced costs in manufacturing through more efficient use of resources, avoidance of hazardous chemicals, reduced number of process steps, etc) to the pharmaceutical industry, in particular amongst high-level managers to drive change within the business.
- Move towards standardisation of methods to quantify the sustainability implications of PPs to facilitate benchmarking between products and processes from different companies including consideration of all stages in the lifecycle of a PP and incorporating energy requirements. These should also be applied to pharmaceutical intermediate suppliers and companies to whom manufacturing steps are out-sourced to ensure greater understanding of supply chains.

- Development of eco-compatibility criteria to score PPs on their environmental impact at all stages of their development including post consumer fate to encourage the pharmaceutical industry to design greener drugs and provide much needed focus on environmental compatibility and end-of-life issues. This could provide a further incentive to pharmaceutical companies if it provided a competitive-edge to PPs that met these criteria over those that did not.
- Use of these eco-compatibility criteria to develop a classification and labelling scheme to provide relevant and practical information for prescribers and users of PPs. This could be based upon an expansion of the Swedish classification and labelling scheme and could be implemented in other countries.
- Lobby for users to give preference to greener drugs (e.g. hospitals/national and local authorities)
- Conduct a study into what would make ecolabels for pharmaceutical products effective and for which types of products in specific (e.g. over-the-counter vs. prescribed drugs). Eco-labels on product packaging for PPs represent a valuable communication method on the environmental impacts of PPs, although this would require a revision of guidelines and legal support.
- Raise public awareness of the issues surrounding the environmental impacts of PPs and the solutions provided by eco-pharmacostewardship approaches through engaging with NGOs and running promotional campaigns. Incorporate education and training of these issues into school and university curricula, as well as Continuing Professional Development for key stakeholders.
- Promote extended responsibility for PPs within producers and distributors. At a European level, EFPIA (European Federation of Pharmaceutical Industries Association) could potentially be a relevant body to promote this concept.

Second challenge of this WP was to review how the impact of a PP can be better monitored following drug authorisation (pharmacovigilance) in order to manage risk and to detect, assess, understand and ultimately prevent environmental impact of PPs.
It was stated that, recently introduced regulatory guidelines for both medicines for human use and those for veterinary use provide structured frameworks in which environmental pharmacovigilance can be approached. Consumption data are important in modelling potential environmental exposure, and are very variable in quality depending on whether compounds are in patent or generic, are prescribed or available over the counter. There are also large variations

between the various European member states depending on the degree of regulation of the provision and use of medicines.

On the other hand, it is important to identify those products of high risk so that monitoring can be targeted in a cost effective manner. The costs of measurements of products in various compartments of the environment are high, and data obtained should be used to help to build and validate robust models that can be used generically. Costs could be reduced where similar compounds can be treated as a set, similar STPs can be grouped, and information on one set of environmental conditions in one region can be used to extrapolate to other similar situations even where they are widely geographically separated. Where possible, tracers can be used as surrogates for compounds that are more difficult to measure. There is a need for a consolidated approach to modelling across Europe, and internationally where appropriate.

Many of the analytical techniques for measuring concentrations in various matrices (some of them complex) are currently based on costly and highly specialised instruments, and are not readily transferable for use in routine environmental laboratories. Some software packages for modelling various aspects of movement, environmental behaviour, and exposure of organisms are available. It is important that these are updated as the knowledge base grows.

Moreover, there is a need to identify existing monitoring methods that can provide reliable and representative information on concentrations in various environmental compartments, and where necessary develop fit for purpose technologies.

Finally, currently there are many potential ecotoxicological assays, all with differing endpoints and sensitivities. There is a need for comparative studies for this range of substances to identify the most relevant, representative and sensitive test species. An area where more work is required is in the assessment of the effects of chronic exposure to low levels of compounds, and the relationship between this and acute toxicity.

Main inputs from KNAPPE events

Four workshops and an International Conference have been organised in order to respectively state the current knowledge and to investigate future options concerning the presence and effect of PPs in the environment.

Workshop 1: Occurrence of PPs in the environment allowed to discuss about (i) Problems and risks associated to analytic methods for pharmaceutical in the environment, (ii) Occurrence of PPs and exposure scenarios and (iii) PPs removal processes

In the light of the presentations and the discussions, it was shown that:

- Modern analytical techniques allow for a very sensitive determination of organic trace pollutants in aquatic compartments. Quality assurance is a key issue for the determination of PPs at environmental level, as matrix effects frequently affect the analytical results.
- Within the different EU-countries, deviations exist in the prescription/consumption behaviour and in the bookkeeping practice for the usage of pharmaceuticals. For example, consumption data are hardly available in Spain and Poland, whereas detailed data exist for France, including even OTC-drugs.
- Modelling of occurrence data is generally feasible for those compounds for which reliable consumption data are available. However, local concentrations might deviate widely from predicted exposure concentrations where non-treated wastewater is discharged or elimination efficiency is low, e.g. due to rainstorm events.
- PPs can be used as indicator substances to determine the wastewater share in surface waters, to determine the input of non or poorly treated wastewater in surface waters, and in general to determine whether a groundwater or water body is influenced by wastewater.
- Source control measures, such as innovations in prescription practice and urine/faeces separation techniques (e.g. in hospitals and public buildings) may lead to an improvement of the current situation, but will not generally solve all problems with anthropogenic compounds in the water cycle.
- The diversity of micro pollutants and transformation products remains a challenge to be tackled.

- Today‘s wastewater treatment achieves only partial removal of pharmaceuticals and other organic trace pollutants. Treatment practice is very heterogenic, as tertiary treatment is not a common standard in the EU. For successful improvement of WWTPs, sewer systems and rainwater overflow systems should be considered as well. State of the art treatment systems, advanced treatment technologies, such as ozonation or PAC (powder activated carbon), are an option but the cost benefit analysis is frequently missing: The precautionary principle seems to be a desirable, but hardly an always feasible way to deal with anthropogenic compounds in the water cycle.

Workshop 2: Ecotoxicology of pharmaceuticals: making sense of the published literature was focussed to assess whether there is evidence for environmental risks, to determine the ecological relevance of the published endpoints and to identify gaps in the knowledge and develop recommendations for future research work. It was shown that:

- A large body of data is now available on the ecotoxicity of pharmaceuticals. This data covers a range of species and endpoints. Data on effect distributions indicates that many pharmaceuticals are not highly toxic to aquatic organisms.
- Generally, reported effect concentrations are higher than maximum concentrations measured in the natural environment suggesting that many pharmaceuticals probably pose a low risk to ecosystems. There are however some exceptions where effects on reproduction and growth and novel impacts have been seen in the laboratory at concentrations close (or lower) than those seen in surface waters.
- A number of ‘novel’ endpoints have been observed in the laboratory. For many of these, it is possible to identify a potential link with ecologically relevant endpoints such as reproduction, growth and predator avoidance. In instances where these novel endpoints are observed at environmentally realistic concentrations, further experimental work is warranted to understand the implications on ecosystem health.
- Existing predictive and extrapolation approaches such as QSARs and the use of acute:chronic ratios are inappropriate for use on pharmaceuticals.
- Pharmaceuticals will occur in the environment as mixtures. For pharmaceuticals of the same class, it should be possible to estimate the combined risk of the mixture using concentration addition calculations. Other approaches may be required for mixtures of pharmaceuticals from different classes.

- Many pharmaceuticals will be metabolised or degrade in the environment. The potential impacts of the resulting transformation products should be assessed. It may be possible to use information on the structure and properties of any transformation product to identify substances that pose the greatest risk to the environment.
- A wealth of data is generated during the development of a pharmaceutical. This data could help to inform the environmental risk assessment of pharmaceuticals.
- Risks of pharmaceuticals in the future might change due to changes in climate (which may result in increased disease pressures) and during pandemic situations.

In a light of above, to fill the observed gap, further works have been identified in order to:

- Understand the ecotoxicity of metabolites and environmental degradation products and approaches need to be developed for identifying transformation products that are likely to pose the greatest risk to the environment.
- Understand the significance of novel endpoints (including results from studies employing proteomics and metabolomics) in terms of their ecological relevance. These studies will help to establish whether or not the standard chronic tests appropriate.
- Consider effects and chemical-based, post-authorisation monitoring of relevant endpoints in the natural environment in order to attempt to understand the impacts, if any, of pharmaceuticals on 'real' systems.
- Understand how risks of pharmaceuticals may change in the future as a result of climate change and pandemics.
- To develop a better understanding of the effects of environmental variables (DOC, pH, nutrients, multiple stressors etc.) on fate and behaviour, uptake and effects to allow better extrapolation from lab to field.
- To compare reported effects data with monitoring data in order to identify substances of most concern. Scientists and industry should be encouraged to share data (table of parameters). Studies yielding 'surprising' results should be repeated.
- Understand whether and how we can extrapolate from mammalian data to environmental effects. The use of contra-indications to indicate potential for ecological risks should be considered and the utility of 'omics' based approaches should be explored for risk assessment purposes. It would be helpful if case studies could be developed for read across from mammalian data to environmental risk for a range of substances.

- Assess the impacts of mixtures of a) pharmaceuticals of the same class; b) pharmaceuticals of different classes; and 3) pharmaceuticals and other substance types.
- Implement long-term studies at realistic exposure concentrations and under realistic environmental conditions.

Workshop 3: Ecopharmacostewardship and ecopharmacovigilance

Over the sessions on ***Ecopharmacostewardship***, a wide variety of existing and new methods for reducing the impact of PPs at all stages in their lifecycle were discussed.

- PPs cannot be addressed as a whole and when considering ecopharmacostewardship approaches, they should be grouped into three different categories:
  - OTCs (over the counter) medicines
  - On patent prescription drugs
  - Off patent (generic) drugs
- The key incentive to drive the development of greener PPs from the perspective of R&D pharmaceutical companies would be patent extension (even for only a very short period). However this is not likely to be well received by generics companies and purchasers of PPs.
- Demonstrating the benefits of increased uptake of green chemistry methods to the bottom line is the best way to drive change within the pharmaceutical industry. Further improvements are still possible, and knowledge transfer within the business e.g. from process chemists to medicinal chemists is one area were this could be achieved. Pharmaceutical companies are only likely to adopt increased use of renewable resources when there is a significant cost driver.
- A move towards standardisation of methods to measure the environmental impact of PPs (to allow comparisons between products from different companies) would be very difficult to achieve and is only likely to happen (in the case of on-patent prescription drugs only) if some method of quantifying the „greenness" of PPs were required from major customers of PPs (e.g. health authorities). In terms of internal measurement of environmental impact of PPs by the pharmaceutical industry it is important that outsourced processes are included in metrics calculations.

- Choice between on patent and generic drugs is true for purchasers, limited for prescribers and non-existent for customers. Choice exists for over the counter drugs. Nonetheless, primary choice remains efficacy; greener drugs may be given preference, but at a secondary level.
- Stockpiling and over prescription of medicines/waste drugs are important issues surrounding the environmental impact of PPs. Health insurers and the National Health Service could drive change in this area through education of doctors, pharmacists and patients.
- The Swedish classification & information scheme for PPs could be extended elsewhere in Europe but this should be done on a country-by-country basis, as and when each country becomes interested. A system implemented Europe-wide, on the basis of the Swedish classification scheme, should be consistent across countries. For its implementation on a broader scale, it is important to clarify several issues, especially the type of data to be used but also the aims of the scheme implementation.
- Since an extension of the scheme to other countries would be a major step, many participants felt that the current Swedish scheme (considered a pilot) should be rigorously evaluated first. It is recommended to first validate the data that the current Swedish classification scheme is based on and to get over some (substantial) technical difficulties before extending the scheme to other countries. Additionally, it is recommended to further assess the value of the Swedish classification system (effectiveness) as well as its expected effects in other countries.
- The benefit of a potential extension of the Swedish classification to the whole pharmaceutical product life cycle was questioned by many participants. The general consensus was that it would be more beneficial to determine qualitatively whether pharmaceutical products had been manufactured in an environmentally responsible way or not.
- Ecolabels on product packaging could, in principle, be applied on PPs merits further consideration. Ecolabels may be of some use on OTC drugs (where there is a choice for consumers) but not on prescription drugs.

Considering ***ecopharmacovigilance***, it was discussed that:

- Substances occur in complex mixtures in the environment, and there may be interactions between them, and these are difficult to predict or measure.
- A post registration reporting scheme for adverse environmental effects of medicines for human use similar to that for veterinary medicines would be a useful safeguard.
- There is a need for new, well designed assays for the ecotoxicological assessment of pharmaceuticals since classical mortality endpoints not applicable for most of these

substances. There would be significant value to be obtained from analyses making direct comparisons between chemical, pharmacological, toxicological, and ecotoxicological data.

- Due to high cost there is a need to focus monitoring efforts on compounds of concern, and different classes of STP.
- There is a need for more careful design of monitoring programmes and toxicological assessments. These need to use more fit for purpose methods (e.g. passive sampling linked with toxicity bioassays), and to make better use of laboratory studies to calibrate and validate field observations.
- A central registry for the collection of data (chemical, environmental, toxicological, pharmacological, and ecotoxicological), and the assessment of its quality and archiving would be a way of reducing cost by avoiding duplication of effort, and assisting dissemination of information. Such a repository of data would help in improving and refining models of the fate, distribution, and environmental behaviour and toxicology. This would help in optimising the use of costly data.
- There is an urgent need to improve communication with the public, and to address (often unfounded) anxieties. This could be a role for the centralised data repository described above.

Workshop 4: Design of instruments to limit pollution from PPs that can be applied to limit the discharge of PPs into the water environment.

It was stated that there is no clear picture yet within industry of potential risks from PPs. However, it cannot be excluded that there *might be* a risk, which is why the use of the precautionary principle is called for in relevant policy discussions. But, it is important to be sure that the appropriate level of scientific evidence of risk be accumulated before costly precautionary measures are invoked.

On the other hand, communication of relevant criteria and more transparency is required for proposed actions, e.g.”why is carbamazepine proposed for priority substance list?” Further it should be clarified which kind of risk should be given priority (e.g. single pollutant or accumulation). In general, the industry (but also government) need to know what is defined as a problem, before it can give an opinion on what types of PPs are of most concern.

In a policy point of view, it is important to identify and to fix the limit to start taking action and to decide if the simple presence of PPs in water is already a problem or should become it. Within this context, also rising costs of possible action need to be considered. In the same line, it was also pointed out that we should differentiate between pollution from peak use of PPs (e.g. in cases of flu, when more PPs are released due to extreme events) and pollution from the systematic use of PPs.

Concerning the ***policy framework***, it was stated that the current policy framework is considered to be sufficient, if allowed to operate properly. There may be some gaps for particular compounds. If there is a class of compounds that has not been tested at all for environmental risk, it was proposed that a representative compound should be tested. Environmental risk assessment (ERA) has to continually improve. In the same time, we should not ignore what we already know; for instance, some studies already exist on chronic exposure effects. However, more information is needed on other issues such as metabolites.

In term of ***good management practices***, possible actions were discussed such as:

- Good prescription practices (e.g. wise use of animal antibiotics in a balanced way for prophylaxis and treatment).
- Environmental classification schemes (such as the one currently run in Sweden).
- Take-back schemes, which are a legal requirement based on EU directives:
  - Take-back schemes are supported by the industry as concept.
  - However, the enforcement of current legislation is still a problem in most countries.
  - An EU guideline on how to set up and operate take-back schemes could further support this measure.
- Procurement and market tenders on the basis of environmental risk criteria: This would involve making large orders of PPs, e.g. by hospitals, based also on environmental criteria.
- Targeted environmental monitoring, e.g. around urban wastewater treatment plants in order to detect risks early. Although there was no general agreement, this was proposed as one possible action.
- Upgrading of wastewater treatment plants:
  - Although limitation of PPs at source should be our first choice, this would not be enough considering the very large amounts of PPs in circulation already (3000 PPs registered).

- The upgrade of treatment plants would also bring benefits in terms of reducing other micro-pollutants.
- However, if action is limited to treatment only (most likely with government financial support), there would be no incentives to change PP release at source.

- Partnerships were also proposed as a good management practice option, e.g. between operators of urban wastewater treatment plants (for whom water pollution with PPs is an "upstream" issue) with pharmacists and doctors in their region to reduce discharge at "source".

The various options proposed for future action have to be assessed on the following:

- Environmental benefits.
- Environmental consequences: e.g. upgrading wastewater treatment raises energy demand in the treatment process.
- Costs: This is related to the fact that no action is cost-free and the issue of shifting costs to options that are more acceptable or less acceptable should be considered.
- Cost-effectiveness.

The ***polluter pays principle***, which is promoted in the field of water protection across Europe, was discussed pointing out the following:

- In the case of water pollution from PPs, who should pay for it? There seemed to be agreement that PPs are a societal problem and the cost should be borne by all, not the supplier or the consumer only.
- In terms of economic instruments that could be used to apply this principle, it was proposed that a sewage treatment fee seems to be the less complex solution.
- It was also commented that market stimulating instruments seem to work better than tax-systems due to the creation of advantages (cf. ecolabels, classification systems). For the way forward, the impacts of both approaches need to be assessed in a more detailed way.
- Finally, it was pointed out that there are many other micro-pollutants in water except for PPs. For this reason, a common approach for all micro-pollutants might be useful:
  - It would/should be a societal decision whether to remove all micropollutants from water or not (in most cases, this being a local or national government issue).

- Although several pollutants would be removed from water, the cost of such additional treatment action could be very high. Relevant costs need to be assessed.

As a ***conclusion***, several areas of further research and future work were identified:

- How to tackle increased PPs in the environment due to population increase & increased consumption? How to ensure that current levels of PP concentrations do not increase further?
- What type of assessment do we need to put PPs on the priority substances list? Should this be based on trends or current concentrations?
- Do take back schemes bring any benefit to the environment? Can this be assessed?
- In general, before applying new policy instruments, much (socio-economic) research is needed to assess the effectiveness of existing management tools.
- What are the costs and benefits of different options? Money should be spent on most effective approaches, which could be take-back schemes, upgraded wastewater treatment and/or additional research.
- Safety levels of PPs in soil (as set in current EU guidelines on environmental risk assessment) may have to be reconsidered, especially in view of new detection findings.
- The evaluation of new drugs might give us some indication & help us reflect back on "old" products with similar modes of action.
- Can we learn more about the behavioural impact of different measures on doctors or vets?
- Finally, research on public risk perception & public risk tolerance would be valuable. This would help us deliver information in a way that is understandable to the public.

International Conference: Pharmaceutical Products in the environment: Trends toward lowering occurrence and impact

The conference aimed to identify new developments and future trends that will facilitate limitation of PPs in environmental waters, and to promote an integrated approach by gathering actors involved with all of the various stages in the life cycle of pharmaceutical products (from manufacture to release in the environment) and providing a forum for discussion. Four conference sessions was organised dealing with:

Session 1: Pharmaceuticals degradation and by products

Session 2: Environmental stewardship for pharmaceuticals: a practical approach

Session 3: Regulatory perspectives: toward environmental priority lists of pharmaceuticals

Session 4: Trends in industrial practices and environmental management

More than 50 works have been presented (conference and posters). Around hundred of participant representing Pharmaceutical Industries, Research Institutes, Sanitary Agencies, Water Companies and other associations attended this event.

The quality of the works presented as well as the interactive discussions between the different stakeholders and scientists will allow the KNAPPE project to propose directive line in agreement with the need and the possible development. A special Issue in Environment International will gather the key findings of this International Conference.

Recommendations from KNAPPE project

Pharmaceutical Products do not appear to be a problem in terms of their environmental impact (up today, there is no evidence of impact on organisms at environmental concentration), 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.

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:

1) 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 PPs***: 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 PPs 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. 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.

Communication and results dissemination

During the whole duration of KNAPPE project, the strategy of communication has been focussed on several audiences and target groups: industrial (pharmaceutical companies), medical (doctor, pharmacist, hospital), social (patient), environmental (water manager, water producer, scientists) and regulatory spheres.
In order to ensure communication and knowledge dissemination, specific actions were implemented such as:

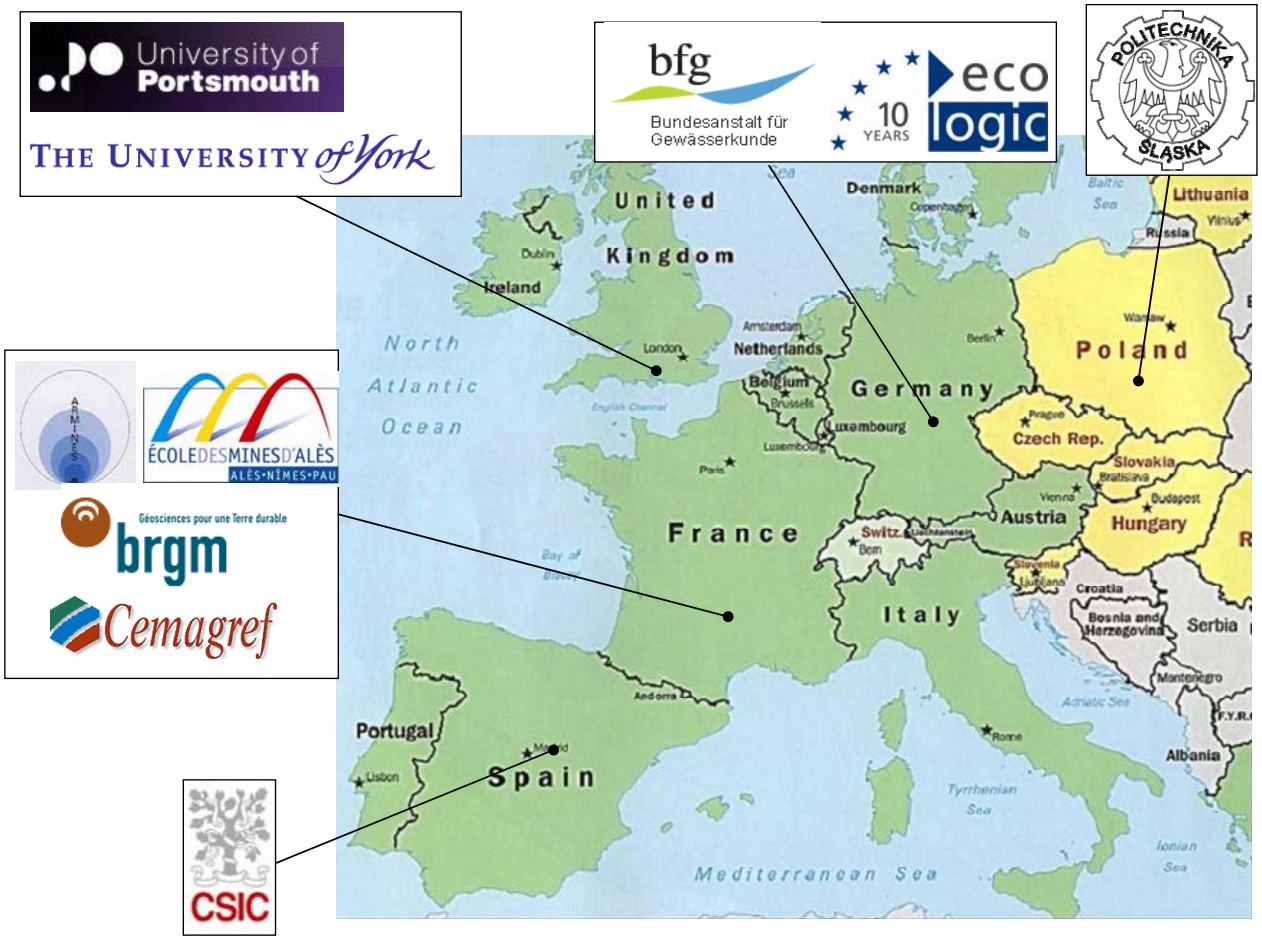
- Web site presenting all the facets of the project and giving available all presentations, deliverables and information coming from the different works performed (www.knappe-eu.org),

- Newsletters addressing technical specific issues for a more advised public. Four newsletters were produced dealing with: KNAPPE project presentation (NL 1), KNAPPE project first findings (NL 2), KNAPPE International Conference report (NL3) and KNAPPE Final Conference report (NL4),

- Information letter addressing the issue of pharmaceutical products in the environment in an easy to understand format and dedicated to the whole community, in particular patients and consumers,

- National and international short press articles allowing increasing public awareness regarding “Pharmaceutical in the Environment” topic.

Consortium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