



Sixth
Framework
Programme

KNAPPE

Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters

Contract n° 036864

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The deliverable authors are responsible for the content

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The objective of the minutes is to report the main conclusions of the different presentations and discussions. All presentations are available on the Knappe web site.

September 8th

B. Roig introduced the session by welcoming all the participants and addressing many thanks to partners and members of the Executive Committee for their works and help during the whole duration of the project.

Then, he reminded the main objectives of the Knappe project progress and introduced the agenda (annex 1). Due to a travel problem, the order of the presentations was a little bit modified.

E. Touraud presented the main outputs of WP6 (communication and results dissemination). She stressed on the important role (participation to Knappe events, outline their expectations, promote discussion and exchanges) of the Executive Committee all along the project and its composition. It was remarked that no medical actors were involved in the Executive Committee, a pity as they represent key actors regarding patient information and their own awareness.

On the other hand, she presented the means displayed for communication and results dissemination within the project:

- Web site: www.knappe-eu.org, where all documents are free to download,
- Newsletters, published every 6 months and stating on the progress of the project,
- Information letter dedicated to increase the public awareness,
- The different events organized during the project: 4 workshops, an International Conference and the Final Conference. Proceedings of these events are available on the web site.
- International and national communications (posters or conferences)

Finally, she announced the next step that will consist in a report of the main recommendations and a CDROM presenting all the documents produced during the project. The CDROM will be sent to all people attending the meeting and to any person requesting it.

S. Zabczynski presented WP2, the aim of which was to report the limitations of conventional treatment processes for PPs removal and new strategies for minimizing PPs discharge in the environment. The main results show that the elimination of PPs by biological processes depends mainly on parameters like SRT (sludge retention time) or HRT (hydraulic retention time) more than on the reactor configuration. Moreover, the nature of the compounds is also important and within a same family, the behaviour of the compounds can differ.

To upgrade the existing WWTP seems to be necessary in order to improve PPs removal such as chemical/physical processes: PAC, GAC (*removal over 80% of x-ray contrast media*) or chemical oxidation processes: UV, H₂O₂/UV, ozonation (*carbamazepine removal over 90%*)

On the other hand, a wide range of protective/proactive actions should be implemented in order to reduce or minimize the introduction of pharmaceutical compounds into the environment such as source control (pollution prevention) and/or source separation.

Few studies concern sludges, and the solid/liquid distribution of PPs. Sorption is one of the significant processes occurring in PPs removal mechanisms and directly linked with the treatment of the sewage sludge. Moreover, landfilling is the most common strategy for sludge disposal (35 – 45%).

Then **D. Loeffler** talked about the occurrence of PPs in the environment and indicators for wastewater originated contamination. During the WP1, an extensive data inventory on PPs regarding consumption and occurrence in the aquatic environment has been established. However, the availability of consumption data and the occurrence of PPs in the aquatic environment on a European level are of very limited comparability. Moreover, a wide data gap on the occurrence of PPs in the different EU countries has been observed as well as for the metabolites and by-products.

Efforts to harmonize EU-Wide measurements should be further extended for sampling, analysis and data evaluation.

On the other hand, a set of indicator substances for (i) the determination of the wastewater share, (ii) finding influences of rarely treated wastewater have been proposed and presented.

E. Kampa presented the main conclusions of WP3 dedicated to Policy perspectives & instrument options. The aims are (i) to review existing policies in EU & selected Member States to limit PP discharge, (ii) to evaluate options for different instruments to prevent & limit PP discharge (regulations, taxes, voluntary tools...) and (iii) to identify further research needs for future instrument selection & design.

After a rapid reviewing of the main regulatory texts, she stated that the current policy framework is sufficient but some gaps exist. There is a need for further investigations (ERA improvement, relation to quality standard, better understanding of data ...). Thus, some actions can be proposed such as :

- Upgrading of wastewater treatment
- Wastewater collection & treatment at hospitals
- Improving the implementation of the current policy framework (ERA (improving data quality & accessibility; testing representatives of non-tested PP classes); PPs in WFD basin characterisation; PPs concentration limits in STP sludge?)
- Take-back schemes (legal requirement): enforcement problems; EU guideline could help
- Implementation of an environmental classification, ecolabels for PPs
- Recommendation for good prescription practices, to consider environmental risk criteria in hospital procurement
- Economic instruments (e.g. sewage treatment fees and/or tax systems).

These propositions need more information on costs & benefits to be gained in ongoing such a project. But currently, not enough information is available for full assessment of all options.

Following, **A. Boxall** commented the conclusions of WP4 dealing with the environmental impact of PPs. The aims of the WP were (i) to review the data on the effects of PPs on aquatic and terrestrial organisms and humans, (ii) to explore the significance of the reported effects in terms of environmental and human health and (iii) to increase the understanding of the impacts of PPs transformation products and PPs mixtures on ecosystem functioning and human health. The works show that:

- A large body of literature is now available on the ecotoxicity of pharmaceuticals,
- Analysis of these standard data (and monitoring data) indicates that risks of most substances (and mixtures) are low,
- Range of subtle effects reported at environmentally realistic levels, many of these endpoints can be related to important ecological functions,
- While traditional predictive approach works poorly for the endpoints of most interest, by drawing on mammalian data and using molecular information, we may be able to identify those substances of most concern and design our risk assessment accordingly.

WP5 dedicated to ecopharmacostewardship and ecopharmacovigilance was presented by **A. Boxall** and **R. Greenwood**. The aims were on one hand (i) to review the role of ecopharmacostewardship across the full lifecycle of PPs and its involvement to improve sustainability, (ii) to investigate classification and labelling strategies, (iii) to give examples of good practices and drivers for an increased uptake of ecopharmacostewardship. On the other hand, dealing with ecopharmacovigilance, the WP aimed (i) to identify the substances/scenarios that should be monitored, (ii) to establish how monitoring can be targeted (develop recommendations on how to design post-authorisation monitoring) and (iii) to identify appropriate post-authorisation monitoring methods – consider range of approaches.

The role of ecopharmacostewardship can be to provide a framework for assessing sustainability/greenness, to promote access to some data available for end of life issues and data for manufacture of pharmaceuticals.

Then, PPs must be split into three categories: On patent prescription drugs, Off patent prescription drugs, Over the counter (OTC) drugs for which, different issues can be exposed in terms of manufacture, use and legislation.

On the other hand, the ecopharmacostewardship studies showed that:

- Pharmaceutical industry must have a driver such as consumer, regulator or cost
- Standardised method for measuring green are needed
- Stockpiling and over prescription have to be evaluated
- Swedish system of classification must be rigorously evaluated before extension to other countries
- Ecolabels may be proposed but it may be more effective on OTCs.

Concerning ecopharmacovigilance, it is clear that substances (3000 medicines in use in Europe) occur in complex mixtures, and interactions between them are difficult to predict or measure. The monitoring is important, but we must design more carefully monitoring programmes and new, well designed assays for ecotoxicological and toxicological assessments (classical mortality endpoints not applicable for most of these substances). However, due to high cost of monitoring, there is a need to focus monitoring efforts on compounds of concern.

Moreover, a central registry for the collection of data (chemical, environmental, toxicological, pharmacological and ecotoxicological) and the assessment of data quality would be very useful.

Finally, there is an urgent need to improve communication with the public needs and to address (often unfounded) anxieties.

The end of the first day was dedicated to a presentation of the French experience in take back scheme from **J. Aumonier** (Cyclamed).

Cyclamed is a non-profit association founded in 1993 that aims to collect unused drugs. Until 2008, Cyclamed tried also to “promote” unused drugs by the way of humanitarian redistribution or energy recovery. Cyclamed is financed by Adelphe organisation which is paying for the packaging wastes valorised with unused drugs collected (1 million €) and by pharmaceutical companies that are paying for drug elimination (3.5 million €). In terms of communication, Cyclamed is very active towards pharmacists (quarterly information letter, Brochure « Good reasons to participate... », attendance to their National Congress) and physicians (joint effort to promote Cyclamed with a comic strip distributed in waiting rooms). Mr Aumonier reminded that Cyclamed has pioneered the take-back scheme area and is still leading the game with 15'000 tons collected yearly. Today, 19 EU countries have implemented take-back schemes for unused medicines.

September 9th

In a first step, **B. Roig** summed up the conclusions of the Knappe project by highlighting the main key points (Pharmaceutical products nature, Consumption and use, Occurrence and Fate in the Environment, Effects/impact, Risk assessment) and presented a series of possible solutions to decrease the presence of PPs in the environment.

These recommendations appeal for five spheres: industrial, medical, social, environmental and regulatory one. Information to doctors and patients, communication between pharmaceutical companies, water companies and researchers, increase of scientific knowledge, evolution of practices (industrial, medical, social) are among the main propositions presented.

Three round tables were organized focussed on social, technical and stakeholders strategies. A general presentation followed by a discussion with the audience was the format of these sessions.

Round table 1: Integrated management strategies for PPs

Florian Keil, coordinator of the START Project (www.start-project.de) presented the main results of the project that focussed on practical options of actions for reducing the contamination of water bodies. The presentation defined three main areas of activity: drug development, handling of drugs and emission controls and detailed actions to be implemented in each of them. Moreover, shared responsibility was promoted rather than polluter pays principle as the latter may results in loss of acceptance. It was further emphasised that precautionary measures must neither hamper innovations in drug development nor impair the quality of medical care.

Finally, the conclusions show that (i) successful risk management requires the integration of measures from all of the three above mentioned areas, (ii) selected measures do not require extensive cross- sector agreements and thus can serve as a starting point for a joint and sustainable effort towards reducing the occurrence of pharmaceutical residues in waters, (iii) the success for such an effort will crucially depend on as many activities as possible kicking off at the same time, (iv) there is a need for proactive engagement of politics at national and regional levels in terms of recognising the occurrence of PPs in waters as a societal problem and (v) the precaution principle has to be considered on the basis of shared responsibilities thus allowing to minimize costs of error and to open potentials for innovation.

After the presentation, the following main remarks have been made:

- Prioritize the actions by using available data can also be pertinent. It seems that prioritization of PPs is important for risk assessment because to look at all groups of PPs will bring too many data, not always the more efficient and relevant. Moreover, investigation on chronic effects and bioaccumulation are required.
- It may be more relevant to speak about effect measurement than risk assessment. There is some lacks of data on chronic compared to acute effects but there is no data on actual effect on environment (synergies, antibiotics, mixtures,...).
- Control and monitoring can be considered, like for other contaminants. As suggested by the WFD, efforts have to be made on selection of cost effective solutions.

Round table 2: Intelligent testing strategy for ERA

Frank Mastrocco presented the principles of ‘Intelligent Testing Strategies’ as described in the ECETOC Technical Report No.102. [<http://staging.idweaver.com/ECETOC/Documents/TR%20102.pdf>]. This ITS methodology describes pragmatic, stepwise prioritization strategies for the selection of test species when assessing chronic effects in environmental risk assessment (ERA). Beginning with an understanding of mechanism of action, ITS considers all existing information on a substance when planning a study in order to use resources wisely and reduce, or replace, the use of fish and amphibians in testing.

The follow on discussion included questions on how to acquire the necessary data and the pitfalls of using QSAR models designed for common chemicals when predicting characteristics of pharmaceuticals. The importance of the selection of the most appropriate effects endpoint as the point of departure for assessing risks was pointed out.

The possibility of industry involvement in ERA for pharmaceuticals in order to take advantage of all the available data on pharmaceutical products was discussed. Establishment of a common database to communicate information to contribute consistency and transparency was also considered.

Several remarks need to be noticed:

- Modelling represents a good alternative to in vivo testing to perform risk assessment studies. It seems a good approach for a screening and may be able to be used to understand chronic exposure. But the system needs to be validated and accepted by the regulation authorities. On the other hand, it requires clinical data that are confidential and then need a good support of pharmaceutical industry.
- QSAR models have been used for other micropollutants, but in a case of PPs, they are not totally effective because they are connected to high uncertainty: e.g. modelling of estrogenicity gives 93% of confidence which is good but not enough to make risk analysis. There is a need to develop specific models for PPs.
- Omics are coming and aim to catalogue action of PPs on receptors and their mode of actions. Thus, omics can't be used alone for indication of exposure because it's very specific on gene expression.

Round table 3: Stakeholder partnership

Richard Greenwood reminded firstly the main stakeholders involved in the life cycle of PPs: pharmaceutical companies, manufacturers of generics, retailers/internet agents, medical and

veterinary professions, patients, governmental organisations, NGOs, legislators, environmental regulators, academic educators/ researchers and general public and stressed on the likely conflict of interests within and between stakeholder groups; it represents the main constraint to a powerful collaboration.

From this introduction, a discussion occurred and the main thoughts allowing gathering stakeholders on common issues are listed below:

- According to the current knowledge, PPs do not appear to be a problem, but that their presence is perceived to be an issue which represents a challenge for management of the environment.

Moreover there is a consensus between the different stakeholders in the need to do something to limit the presence of PPs 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 to mainly lack of data) or considered as limited, there is no urgency to act. The question is how to assess the real risk?

- Current ecotoxicology data show that acute effects at the concentration found in the environment are negligible but some PPs present an effect and few data are available concerning mixture and chronic effect. Thus, data concerning impact of PPs have to be increased and the molecules of interest have to be prioritized for further investigation.

- The communication between stakeholders needs to be promoted by a European network. Moreover, identify the priority topics for stakeholders will promote international dialogue.

- Drinking water companies have to be highly involved because they are responsible of the distributed water and they are subjected to a strong pressure from public even if there is no proof of impact of drinking water on human health, in particular at the current concentrations. However, public do not want to drink water containing contaminants even if these contaminants are not dangerous. It seems difficult to convince people, but efforts have to be made, with a proper communication, relevant explanation by all stakeholders, to mitigate fears. On the other hand, it seems that people agree to pay for cleaning water.

- Information of doctors and patients is a crucial issue. But, if the doctor can prescribe medicine with less environmental impact, who has to decide? Patient or doctor? Patient can insist on this or not. It is the same issue as for generic substitution. Patient got the choice but in France has to pay more for the brand molecule.

- The improvement of take back scheme at the European level is an important issue.

As a conclusion, the discussion moved towards the next step and the ways to go forward in this problematic. Knappe will provide a series of recommendation that will need to be prioritized. Effect on human bodies, bioconcentration, chronic effects are parameters for such a prioritisation.

On the other hand, these recommendations will have to be supported by very practical propositions allowing to implement them at national or international scale or to rely them (if possible) to initiatives already launched (take back scheme, data collection, classification, ...).

ANNEX 1: AGENDA OF THE FINAL MEETING



Knowledge and Need Assessment of Pharmaceutical Products in Environmental waters

FP6 European project Contract n°036864

www.knappe-eu.org

KNAPPE Final conference
8-9 September, 2008, Armines Ecole des Mines Paris, France

Conference Day One: Monday 8 September 2008

13.30 Registration

14.00 Introduction (B. Roig)

Session 1: Knappe presentation of results

14.15 Occurrence and fate of PPS in different environmental compartments (D. Loeffler, S. Zabszinski)

15.00 Environmental impact of PPs (A. Boxall)

15.30 Coffee Break

16.00 Regulatory perspectives (E. Kampa)

16.30 Environmental stewardship and ecovigilance (S. Breeden, R. Greenwood)

17.15 Communication and Result dissemination (E. Touraud)

17.45 General discussion

18.00 Cyclamed : the leading experience in French take-back schemes for medicines (J. Aumonier, Cyclamed)

18.30 End of the session



KNAPPE

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8-9 September, 2008, Armines Ecole des Mines Paris, France

Conference Day Two: Wednesday 9 September 2008:

09.00 : Knappe Synthesis (B. Roig)

Round tables

9h30. Session 2: Integrated Management strategy for PPs

Chairman: Florian Keil, Institute for Social-Ecological Research ISOE GmbH, Frankfurt

11.00 coffee break

11.15 Session 3: Intelligent Testing strategy for ERA

Chairman: Valeria Dulio (INERIS) and Paul Houeto (AFSSAPS)

12.45 Lunch

14.30 Session 4: Stakeholders partnership

Chairman: Richard Greenwood (UoP)

16.15 Final conclusion

16.30 End of conference

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