



Sixth
Framework
Programme

KNAPPE

Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters

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B. Roig introduces the session by addressing many thanks to EFPIA for its welcome in their building and for the facilities it offers in the organisation of this meeting.

This second Executive meeting offers the opportunity to include in the stakeholders group new members (Lyonnaise des Eaux, Janssen Pharmaceuticals, AFSSA, private hospital association).

B. Roig reminds that the Executive Committee (EC) is composed by external members identified as stakeholders and « beneficiaries » of the project and include representative of pharmaceutical industry (human and veterinary), water companies, various associations, ... The role of these stakeholders is to participate actively to KNAPPE events (meetings, workshops, conferences), to validate the KNAPPE programme strategy and to give their opinion concerning the work done in relation with their expectations. They can also be a support of the project by promoting the discussions and exchanges.

Concerning the different events, 3 main periods need to be distinguished: in month 12, the organisation of 2 workshops and an international conference for which the participation of the members is welcomed as well in month 15 and 18 during two other workshops and the final conference respectively. Moreover, every 6 months the EC is gathered to discuss the progress of the project.

Finally, **B. Roig** presents the current way of communication allowing the diffusion of the project. The first one is the implementation of the website (www.knappe-eu.org) in which all the documents in relation with the project (description of works, newsletters, deliverables, meetings minutes) can be freely downloaded. Another procedure has been launched in France with specialised press by sending to about 100 journals an article presenting the project. Several journals have published this article in the former form and others have contacted the coordinator for more information and details.

Finally, two communications are planned in ERAPHARM final conference (29-21 September 2007 in York – UK) and in Environmental Risk Assessment of Human & Veterinary Medicines (25 – 26 September in Berlin- Germany).

After the introduction, **M. Schluesener** and **S. Zabczynski** presented the first outputs of WP1 and WP2.

WP1 concerns the occurrence of PPs in the Aquatic Environment towards indicators for contamination with pharmaceuticals. The participating institutes are BfG, Armines, UoP, CSIC, BRGM, Cemagref. The objectives are mainly to propose a list of the most relevant PPs, to identify the data gaps and to propose indicators of contamination.

The first part of the work was to collect numerous data from (i) pharmacological and physicochemical properties, (ii) fate and exposure, (iii) national reports, Ph.D.-Theses, national scientific literature, (4i) national consumptions in different countries (from 1998-2006), (5i) drug prescriptions, usage in hospitals, non-prescriptive drug, diagnostics

The excel file aggregating these data is presented.

At this time, data concerning national consumption and metabolism are missing.

Based on the first data (annual consumption in EU, occurrence in scientific communications and national databases), about 120 molecules (and metabolites) can be defined. This list needs

to be adjusted by taking into account other parameters. A first analysis shows that, among the different pharmaceuticals consumed, we need to differentiate those easily metabolised by human body, and that are not found in the environment unlike their metabolites (example of metamizole and its derivative 4-Acetamidoantipyrine).

On the other hand, some pharmaceuticals are easily degraded by classical wastewater treatment plants as for example ibuprofen and paracetamol and can be good indicators of the efficiency of STPs. Some others are difficult to eliminate (carbamazepine, AAA, iodinated contrast media) and might be appropriate to elucidate the proportion of municipal treated wastewater.

Finally, other molecules, mainly consumed in specific places can be good indicators of the source of release (for example vancomycine and cytostatic drugs might be useful to identify the hospital share)

WP2 is dedicated to the assessment of limits of the current water treatment processes and new developments for the removal of PPs from water. In a first time, delineation of the factors that determine PPs susceptibility to conventional treatment processes used in sewage treatment plants (STPs) and for more advanced treatment has been carried out:

- sludge retention time (SRT),
- hydraulic retention time (HRT),
- reactor configuration (conventional activated sludge process, conventional activated sludge process – carbon removal only, membrane-assisted bioreactor, sequencing batch bioreactor, fix-bed reactor)
- redox conditions (anaerobic, aerobic, anoxic, overall or mixed)
- biomass concentration.

It has been illustrated for each pharmaceutical group with the most resistant compounds: antibiotics (fluoroquinolones), anticonvulsants (carbamazepine, valporic acid), antidepressants, antiinflammatories (ibuprofen), β -blockers, contrast media, hormones, lipid regulators, and tranquilizers

The main conclusions are the following:

- SRT is the most important parameter influencing the PP removal – in most cases „the nitrification sludge age” (10 – 20 days) is enough to transform the majority of the compounds (except for contrast media, anticonvulsants);
- SRT is the parameter, which determines the biodiversity of the biomass, predominant bacteria in the active biomass and their enzymatic activity;
- HRT also plays the main role in the PP removal, the average value of the parameter (above 12 h) seems to be enough to increase the transformation of the substances (exceptions: contrast media and anticonvulsants);
- Conventional activated sludge process – carbon removal only showed poor PP's removal;
- The performance of the SBR (sequencing batch reactor) shows to be the optimal reactor configuration in the PPs transformation (combination of the anaerobic, anoxic and aerobic zones, especially 12 h cycle);
- No significant difference in the performance of the onventional activated sludge process and membrane-assisted bioreactor (exception: contrast media).

Differences according to climate zones (Germany, Austria, Spain, England, Sweden/Finland, Australia, Japon, USA/Canada) and the influence of temperature on PP removal in a sequential batch reactor have been studied:

- The varying removal rate with regard to regional specificities – linked rather with patterns of PPs consumption in each region than climatic zone
- The raise of the temperature seems to increase the transformation rate of some compounds.

Lacks of data in several categories have been pointed out. It concerns especially redox conditions (combination of the zones could have the huge influence on the PPs removal, e. g. contrast media).

Concerning the biodegradation kinetic, two observations can be done:

- The reaction rate constant is expressed per sludge dry matter concentration, it not only depends on the degradability of each specific compound, but also on the sludge composition, (biodiversity of the biomass and their activity, fraction of active biomass within the total suspended solids, floc size of the sludge and free-swimming bacteria....=> SRT),
- co-metabolism – it is speculated that some PPs are being degraded by enzymes produced for other primary purposes. The micropollutant transformation could be due to nitrifiers being active in the activated sludge.

A discussion succeeded to these two presentations and highlighted and clarified the following points:

- the consumption data are of concern for all countries, or at least the major European countries (UK, Germany, Spain, France, Poland). But these data are not easy to obtain. **M. Murray** (ABPI) and **M. Poulmaire** (EFPIA) will try to give information from UK and other European countries, respectively. The same question exists for hospital consumption and **V. Molières** (C2DS) will try to have information concerning consumption in specific hospital establishments in France.
- it is relevant to evaluate the gaps between consumption data and the occurrence in the environment even if it is difficult to make a relation
- the water flows of the receiving surface waters may be quite important for the comparison of the data on the presence of PP in natural waters because the dilution of the discharge into the receiving water body may be quite variable
- the relation between data concerning sold and consumed medicines could be interesting to be investigated but it will be dependent of the drugs and also of the difficulty to find data in terms of use. However, even if all pharmaceutical companies have a picture for their products according to the sale in the different countries, it's difficult to have a global overview at the worldwide.
- the compilation of the data are interesting but stakeholders need to examine closely the different items compiled in the review and to evaluate the lacks in function of their own expectation. The relation with the environmental effect of pharmaceutical will be an added value for these data. Moreover, a connection with Norman will be interesting in particular to integrate data concerning analytical performances of current laboratory methods and to home the whole data.
- the “degradation” term includes the different modes of elimination of pharmaceuticals and do not distinguish biological degradation, chemical elimination, sorption, ...
- the data presented on the efficiency of various STP processes need to be accompanied by information about the number of treated data in order to estimate the representativeness of the data
- the project focus mainly on human pharmaceuticals because it is more relevant for urban wastewaters. However, even if the way of exposure is different between human

and animal pharmaceuticals, in France for example, 60% of farms are connected to WW network for the liquid manure and the use of liquid manure for fertilizers is decreasing strongly. Concerning consumption of veterinary pharmaceutical, **E. Miceli** was asked to check if some data are available.

- Concerning the treatment processes, the climate parameter seems to be not very relevant whereas the mean water temperature in STP could be a better parameter to include in the examination of the STP efficiency. For example in Poland, there is big difference between STP efficiency in function of mean T° in winter and summer whereas in Switzerland, these differences were less observed. On the other hand, there are few data concerning the evaluation and variation of the STP efficiency during long period of time (M. Schluesener offered to provide data from an on-going thesis dealing with this issue).

Finally, in the next works, other processes (than biodegradation) will be investigated such as Advanced Oxidation Processes (AOP), Fenton process, and data concerning treatment for drinking waters will be also collected.

E. Touraud made a brief presentation of actions in WP6. The web site is implemented; the first newsletter has been achieved in March 2007 with an editorial written by David Taylor (EFPIA) showing the involvement of pharmaceutical industry in Knappe project. The second newsletter is in preparation with an editorial of Christian Daughton untitled "Pharmaceuticals in the Environment: Why Should Anyone Care?". First results obtained in WP1 and WP2 will be highlighted.

She stressed on the preparation of the International Conference and of WS1 and WS2 workshops: 3 days (18-19-20 February 2008) in Nîmes. A first call has been made in March 2007 but one needs to enlarge the information dissemination by:

- Next call : September 2007
- Press file to diffuse in the press in partners countries (it has been done in France)
- Call and leaflet of the International Conference on the partners and stakeholders websites and information through contacts networks (leaflet is on Knappe website)
- Sessions chaired by invited speakers : partners and stakeholders proposition are welcome
- Plenary lectures will be done by Klaus Kümmerer (Germany), Ake Wenmalm (Sweden), Ettore Zuccato (Italy), Ilene Ruhoy (USA), Florian Keil (Germany)
- Special issue in Environment International

WS3 and WS4 are planned in month 15 (end of April 2008). They will probably be held in York. Plenary lectures will be done by invited speakers.

M. Cronin spoke on behalf of SCI, Society of Chemical Industry which agrees to help in the organisation but need to finalise their contribution.

E. Kampa presented the organisation of WP3 which started in month 6. The key objectives are:

- To gather information on existing regulations and incentives (e.g. taxes) at European levels and selected member states on pharmaceutical products discharge: the work is in progress. The next step is to identify the gaps in the current approaches used (this work will be finalised by December 2007)

- To assess and propose options for a future European approach: this work will be based on literature review, stakeholders interviews. The expert workshop (WS3) will be the place to discuss interim proposals.

E. Kampa proposed to involve stakeholders in the two activities by:

- Giving ideas on good practice examples on legislation and incentives,
- Acting as interview partners on the design of instruments and participating in the expert workshop (WS3).

M. Murray indicates that he was concerned at the implication that Ms Kampa gave that some form of Regulation of pharmaceuticals in the environment was necessary. This before there had been any assessment by the other aspects of the study as to whether there was a problem to regulate.

P. Michoux explained that there is an environmental risk assessment as part of the medicines authorisation process and this is clearly defined in the EMEA guidelines available on its website.

The countries with the most experience in environmental risk assessment for pharmaceuticals are the UK, Sweden and Germany in Europe and also Canada.

The third Executive Committee will be organised in Brussels (EFPIA building), the second week of January. The date will be communicated.

ANNEX 1: AGENDA OF THE EXECUTIVE COMMITTEE

July 17 2007, Brussels

13:30	Introduction <ul style="list-style-type: none">- Time schedule- Deliverables and events- External communication-	B. Roig
13:45	WP1 achievements presentation & discussion <ul style="list-style-type: none">- Data acquisition and exploitation- Synthesis of results- Choices of parameter of selection- Selection of most relevant PPs- Lacks	D. Loeffler
14:30	WP2 achievements presentation & discussion <ul style="list-style-type: none">- Information acquisition- Current processes and their limits- Trends of new developments and practices- Lacks	S. Zabczynski
15:15	WP6 achievements presentation & discussion <ul style="list-style-type: none">- Newsletter- Information letter- CD Rom- Workshop and international conference	E. Touraud
15: 45	WP5, WP4 & WP3 presentation and discussions <ul style="list-style-type: none">- Objectives- Actions-	E. Kampa A. Boxall J. Clark
16:30	Conclusion	B. Roig
16:45	End of the meeting	

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