

### 3) Industrial practices

Pharmaceutical industries and healthcare structures are fully involved in the presence of pharmaceutical products in the environment and work on their practices in order to mitigate their responsibilities. **D. Taylor** (AstraZeneca, UK) explained that, in an ecopharmacostewardship perspective, EFPIA Member Companies are minimising releases from manufacturing and are continuing to improve predictive environmental risk assessment. Medicines under development today, are likely to produce lower environmental residues than the current generation of products. **S. Breeden** (University of York, UK) outlined the environmental issues around pharmaceuticals manufacture, use and disposal as well as the drivers for change in their life cycle. He looked at the methods for measuring environmental credentials and identifying problems and solutions to those issues (renewable resources, bio-derived solvents, clean synthesis techniques...). On the other hand, the design of 'green' pharmaceuticals remains an enormous challenge. Green chemistry has been introduced in several pharmaceutical industries as for example in Pfizer. **P. Dunn** (Pfizer, UK) showed the redesign of new drugs synthesis (i.e. Pregabalin) by including biotransformation reaction or green solvents. Moreover, Pfizer, as a member of the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable, sponsored Green Chemistry research. Green pharmacy can be also a good opportunity to act in the reduction of PPs in the environment as explained by **K. Kümmerer** (Frieburg, Germany). The rational design is to include the whole life cycle of a compound through life cycle assessment tools. This will lead to a different understanding of the full functionality necessary for an Active Pharmaceutical Ingredient.

As a conclusion, industrial and healthcare practices changes are an actual challenge for society because one has to consider the balance between the benefit for the patient and any potential environmental impact of a pharmaceutical.

### Conference participants

**Pharmaceutical Industries:** Lundbeck A/S (Denmark), Sanofi Aventis, Merck Santé, Bristol Myers Squibb (France), Abbott, Bayer Healthcare, IBACON GmbH (Germany), Allergan pharmaceutical (Ireland), Apoteket (Sweden), F.Hoffmann-La Roche Ltd (Switzerland), Astrazeneca, Eli Lilly and Company Limited, GlascoSmithKline, Wyeth, Pfizer (UK), Johnson & Johnson, Merck & Co., Inc. (USA)

**Research Institutes:** VITO (Belgium), Health Canada (Canada), BRGM, Cemagref, EHESP, Ineris, INPT (France), Ecologic, Institute Social Ecological Research, Institute of Environmental Research, Federal Institute of Hydrology (Germany), Institute for Pharmacological Research (Italy), NIVA (Norway), CSIC (Spain), Royal Institute of Technology, IVL Swedish Environmental Research Institute (Sweden), EAWAG (Switzerland), KIWA (The Netherlands)

**Universities:** Mc Gill (Canada), Limoges, Provence, Paris Sud (France), Freiburg (Germany), Torino (Italy), Kyoto (Japan), Silesian (Poland), Evora (Portugal), Liverpool, York, Portsmouth (UK)

**Sanitary Agencies:** AFSSA, AFSSAPS (France)

**Water Companies:** Veolia Environment, SAUR, Suez Environment (France), Grontmij|AquaSense (The Netherlands)

**Associations :** EFPIA (Europe), LEEM (France), ABPI (UK), EPA (USA), SCI, SETAC (Worldwide).

### EDITORIAL

*At the time when the sustainable development is more and more considered, questions of safety and environment are fully included in all industrial activities. The problematic of Pharmaceuticals in the Environment, even if is no longer a new issue (lot of works since the 1990s) became a priority concern because of the potential impact drugs represent both for aquatic and terrestrial organisms. In the context of the high evolution of analytical techniques (allowing the detection of more and more substances), the development of new processes of decontamination, the evolution of regulation (WFD envisages to add 5 pharmaceutical substances to the list of priority substances) and industrial practices (both in pharmaceutical companies and in healthcare daily attitude), Knappe project was launched to establish a state of the art of the current knowledge and then to propose actions to reduce the occurrence and impacts of pharmaceutical products (PPs) in the environment.*

*A focus on new approaches was also proposed to complement this overview and delineate the future and most promising first actions to be carried out. The International Conference entitled: "Pharmaceuticals in the Environment: Trends toward lowering presence and impact" has been organised in Nîmes on February 19-20<sup>th</sup>. One hundred of participants discussed and debated around four sessions of conferences and posters exhibition. More than 50 works have been presented. Representatives of 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.*

*Finally, I would like to express my gratitude to all participants for their involvement and their support.*

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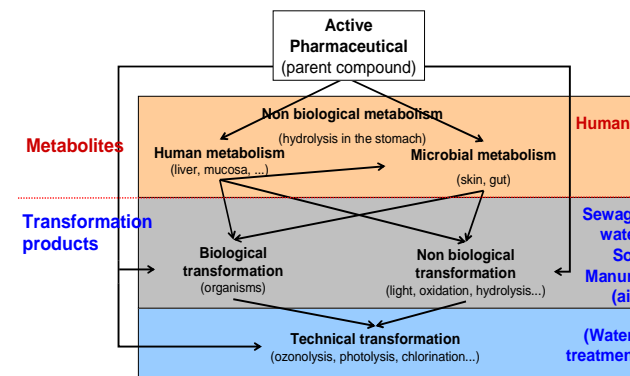
Organised in four sessions managed by international experts, the conference aimed to promote discussions about: (i) Metabolites and transformation products of pharmaceuticals in the environment : occurrence, toxicity et potential risks, (ii) Environmental priority lists of pharmaceuticals : the different attempts in Europe, (iii) Ecopharmacostewardship: the role of the key stakeholders (pharmaceutical companies, patients, regulatory bodies), some practical approaches, how to move towards an integrated risk management strategy, and (iv) Towards green pharmacy: green chemistry in the process development, life cycle assessment of molecules.

As a conference introduction, a first overview of the problematic in USA was given by **S. Glassmeyer** (EPA, Cincinnati, USA). She presented the major research activities of USEPA in the implications of pharmaceuticals and personal care products (PPCPs) as environmental contaminants. The scope of research includes development of analytical methods for monitoring PPCPs in waters, sediments, sewage sludge and tissues, examining of their impact on aquatic systems, investigating the significance of drug disposal and analyzing treatment technologies to minimize the release of PPCPs into the environment and their “recycling” in drinking water.

Then 3 aspects were more specifically presented and discussed:

### 1) Metabolites and transformation products (MTP)

Many pharmaceuticals undergo a structural change in the body of humans and animals, resulting in metabolites which differ in both pharmacological and toxicological properties compared to their parent drugs. In addition, many pharmaceuticals are bio-transformed by organisms such as bacteria and fungi in the environment. To draw a distinction between this terminology is an important issue in order to consider the behaviour of the parent molecule in the environment. **K. Kümmerer** (Frieburg – Germany) specified this terminology as illustrated in the opposite figure. As by metabolism, the chemical structure of the active molecules is changed during these transformations. Several parameters and relevant endpoints are necessary for appropriate interpretation. On the other hand, the presence of this “daughter” molecule has to be considered in the line of the (eco)toxicity power of pharmaceutical molecules.



In term of risk assessment of metabolites and transformation products, **A. Boxall** (York University, UK) made a parallel with previous studies and feedback on pesticides and derivatives and addressed several major questions that have to be taken into account: (1) What is the environmental behaviour of MTP compared to the parent compounds?, (2) What are the effects of MTP on organisms?, (3) How can we identify substances of potential concern?. Then, even if a ‘total residue approach’ is unsound, there is a need to assess transformation products presence and impact and, for intelligent assessment schemes, to proceed to more time- and cost- effective monitoring procedure.

### 2) Environmental management & control

The first outcome of Knappe project concerning measurements and removal options in European wastewater treatments plants was in a second time presented. **T. Ternes** (BfG, Germany, Leader of KnappeWP1) showed a first inventory (based on current literature) of the most relevant pharmaceuticals (181 PPs) for the exposure of the aquatic environment. By compiling this compilation with data on performance of treatment plants, nature of water, some environmental indicators could be proposed for environmental management. For example, carbamazepine, erythromycin and iopamidol (very low degraded) could be proposed for the share of treated wastewater in surface waters; paracetamol and ibuprofen for input of widely untreated sewage, with respect to the removal organic trace pollutants. Indicator substances could be available for wastewater, but still missing for unwanted ecotoxicological effects. Advanced removal options (activated carbon adsorption, ozonation, ...) for micropollutants removal in WWTPs are feasible, but the cost-benefit analysis is missing.

Dealing with pharmaceuticals management, the Swedish experience, in order to introduce more environmental cautiousness in the European directives on evaluation and authorisation of medicinal products within the community has been highlighted. An international reference group for “the Swedish initiative” has been constituted. **A. Wenmalm** (Stockholm County Council, Sweden), presented the risk and hazard classification of pharmaceuticals, developed jointly by the Pharmaceutical Industry (LIF), Apoteket AB (owner of all the pharmacy shops) and SCC (provider of public health care in Stockholm region). To date, about 40% of the pharmaceutical substances on the Swedish market have been classified, constituting 65% of the sales volume of pharmaceutical products ([www.fass.se](http://www.fass.se) and [www.janusinfo.se](http://www.janusinfo.se)). All substances are expected to be classified in 2010. This successful initiative allows suggesting introduction in all EU. In the same frame, **M. Mons** presented an international priority list of pharmaceuticals relevant for the water cycle, developed with the support of the Global Water research Coalition. 153 compounds have been regarded using 17 different criteria. The number of criteria has been reduced to the seven most relevant for prioritization, according to expert judgement and evaluation and led to a classification into three categories of 10 (high), 18 (medium) and 16 (low) priority pharmaceuticals. IVL Swedish Environmental Research Institute (**A. Woldegiorgis**, Sweden) provided the experiences gained through the environmental risk assessment program for human pharmaceuticals. The basis of the classification is the PEC/PNEC equation governing the risk phrase associated with the pharmaceutical. Comparison between PECs (predicted environmental concentration) and MEC (measured environmental concentration) indicates that the PEC equation used in the [fass.se](http://www.fass.se) system is mostly in accordance with the precautionary principle.

In the line of environmental management of pharmaceutical product, precautionary principle as well as risk management strategy have been mentioned by **Florian Keil** (ISOE GmbH, Germany) coordinator of *start* project ([www.start-project.de](http://www.start-project.de)). Considering the full life cycle of a pharmaceutical product, the project investigates three areas where solutions for reducing its occurrence in the water cycle: drug development, drug use and emission management. An integrated approach allowing different actors of the three areas a joint risk management based on shared stewardships is required. The guiding theme of this approach is to frame precautionary action such that it promotes social and technical innovation.