



Status and Potential of "Green Pharmacy"

Kümmerer, Klaus

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Pharmaceuticals in the environment

Results of an EEA workshop

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European Environment Agency
Kongens Nytorv 6
1050 Copenhagen K
Denmark
Tel.: +45 33 36 71 00
Fax: +45 33 36 71 99
Web: eea.europa.eu
Enquiries: eea.europa.eu/enquiries

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Foreword

A decade ago, the EEA and others first drew attention to the environmental impact of pharmaceuticals. Since then awareness has increased and research projects funded by the EU and others have expanded understanding of the use, exposure, fate, accumulation and impacts of pharmaceuticals in the environment.

To help assess and disseminate the research findings to date, the EEA organised an expert workshop in January 2009. The workshop's conclusions, set out in the present report, highlight the need for action to improve further our understanding and management of risks.

The situation looks worse than a decade ago

Compared to 1999, **there are grounds for increased concern**. We now understand better the potential eco-toxicity of many pharmaceuticals and mixtures of medicines that enter the environment during their production, consumption and disposal, albeit in very small quantities. In addition, it's apparent that per capita consumption of medicines is increasing, monitoring and controlling pharmaceuticals' entry into the environment is difficult, and some wastewater treatment techniques have shortcomings.

The situation is likely to deteriorate further as ageing populations demand ever more medicines, and persistent or bioaccumulative compounds build up. This is despite the reduced environmental impacts to be expected from more personalised medicine and biopharmaceutical advances.

Research results have confirmed that both human and veterinary medicines pose environmental risks, and some eco-toxicity data indicate that the concentrations found in the environment have detrimental effects. But the increasing number of relevant research projects could be rendered more useful if there were a European database of projects and results.

We need to look at impacts across the whole life cycle

We need to move from environmental risk assessment of a few drugs to far more comprehensive **environmental stewardship of pharmaceuticals across their full life cycles**, including manufacture. Without such a holistic approach there is a real danger that reduced environmental impacts at end of life might mask other harm to the environment that can arise before the product reaches the pharmacy.

A life-cycle approach means looking at pre-production issues (including raw materials and energy), secondary manufacturing, and the impact of drugs and their breakdown products when they enter the environment. By broadening the analysis of environmental impacts to include the full life cycle, we can reduce environmental footprints. And by identifying hot spots we can develop ways to avoid especially harmful or inefficient activities.

We need greener pharmacy, based on appropriate technologies and incentives

Growing awareness of environmental impacts and the need to conduct tests to evaluate such effects are creating cost pressures for the pharmaceutical industry, incentivising the development of **greener pharmacy**. As the ratio of waste to useful product is very high in the pharmaceuticals sector, there is considerable need for greener pharmacy innovations that are 'benign by design'.

It may well be that the patent system could be adapted to encourage pharmaceutical companies to address environmental impacts alongside medicinal effectiveness in their research and development programmes. Extending the patent duration for pharmaceuticals that are 'benign by design' could boost incentives to develop substances with less environmental impact.

We need improved waste management

Used and unused pharmaceuticals have considerable implications for **waste streams**. The technical and economic burdens on both urban wastewater treatment and household waste management are considerable. This will have policy implications, bringing into question EU funding, full cost recovery via water treatment pricing, and the nature and efficiency of 'take back' schemes for unused medicines.

A recent EEA survey of take back schemes in the EU and some other countries showed large national variations in the amounts that households returned to pharmacies and in the effectiveness of schemes. Based on the positive experiences at local levels, an EU-wide take back scheme via pharmacies should be established. And it should be complemented with improved **labelling** of hazardous pharmaceutical substances and the **classification** of pharmaceutical wastes as hazardous. Such measures could help improve public awareness and encourage more cautious prescription of medicines.

And we need robust information to guide the public and policymakers

The general public and researchers have limited access to data and information on patterns of use, exposure scenarios and potential hazards of pharmaceuticals. The pioneering use of an environmental risk classification scheme for several hundred pharmaceutical products in the Stockholm area is already proving useful for both health professionals and patients. It could be extended across Europe, with country-specific adaptations.

As is already the case for veterinary medicines, **risk-benefit analysis of pharmaceuticals should**

incorporate environmental risk assessment. More data on environmental effects should therefore be provided during the authorisation process. Furthermore, priority should be given to substances that are of environmental concern and whose risk has not been evaluated.

Further research into potential environmental impacts is clearly needed, especially for non-standard effects, metabolites and transformation products, and mixtures of pharmaceuticals. There is already evidence that the aggregate toxicity of mixtures is sometimes substantially higher than the toxicity of individual substances.

Notwithstanding the new research results summarised in this report, there continue to be **very few data on the environmental exposures, fate and impacts** of most pharmaceutical products. This implies the need for the enhanced **monitoring** of substances, especially in water but sometimes in sediments. Such monitoring should focus on priorities such as antibiotics, antiparasitics, hormones, analgesics and psychotropic medicines, especially those released into the environment in large quantities and expected to have environmental effects. Such monitoring will need to be supplemented with **water quality guidelines** for priority substances.

Medicines continue to provide enormous benefits to all of us and will be increasingly necessary as people live longer. We must recognise, however, that these benefits could be offset if we ignore pharmaceuticals' environmental impacts. Besides helping protect humans and the environment, taking action now to limit and better understand the risks could help boost eco-innovation.

Jacqueline McGlade,
Executive Director

Acknowledgements

This report summarises the results of a workshop held at the European Environment Agency, Copenhagen, on 13 and 14 January 2009. It benefits from the presentation summaries prepared by the speakers, representing a wide range of expertise.

On the basis of the speeches and subsequent discussion of the issues, Gerald Vollmer (EEA)

prepared the executive summary and the conclusions chapter in cooperation with David Gee (EEA). Those chapters benefited from the comments of speakers and participants, and of EEA staff, in particular Dorota Jarosinska, Almut Reichel and Jock Martin. The EEA thanks Joop De Knecht for chairing the workshop.

Introduction

The European pharmaceutical market has been growing for decades and the environmental impact of pharmaceutically active substances has increased in parallel.

A decade ago, the European Environment Agency (EEA) identified the subject as an important emerging issue in its report 'Environment in the European Union at the turn of the century'. Since then, ever more research and expert recommendations^(1,2,3) have underlined the need to tackle the release of pharmaceutical substances into the environment, primarily via wastewater.

To extend awareness of this emerging issue and to help achieve significant and measurable improvements in Europe's environment, the EEA

invited experts from the science, industry and state sectors to participate in a dialogue. The aim was to improve information exchange and reach common positions on the current situation and necessary improvements.

The EEA hosted the expert workshop on pharmaceuticals in the environment in Copenhagen on 13 and 14 January 2009. The workshop addressed a variety of issues, including the magnitude of the pharmaceuticals market and the amounts of pharmaceutically active substances produced; the pathways by which active substances enter the environment; detected or assumed environmental effects; and ways to reduce impacts. Recognised experts spoke on each of the issues and summaries of their contributions are presented in this report.

⁽¹⁾ German Advisory Council on the Environment, 2007. Pharmaceuticals in the Environment. Statement April 2007. No. 12. Available at: http://www.umweltrat.de/english/edownloa/statemen/Stellung_Pharmaceuticals_in_the_Environment_2007_eng.pdf [Accessed 10 June 2009].

⁽²⁾ KNAPPE project report: see the summary of the presentation by B. Roig in Chapter 6 of the present report.

⁽³⁾ Kümmerer, K., 2008. 'Strategies for the Reduction the Input of Pharmaceuticals into the Environment'. In: Kümmerer, K. (ed.) Pharmaceuticals in the Environment. Sources, Fate, Effects and Risk. 3rd edition, Springer Publisher, Berlin Heidelberg New York, 433–440.

Summary of the workshop

On basis of the speeches given and debates during and at the end of the workshop, the experts agreed to describe the situation as follows:

Pharmaceutical substances are due to their inherent properties in humans **biologically active** and often engineered so that they remain unchanged during their passage through the human body. Unfortunately, this stability means that they also persist outside the human body, which can create environmental problems.

For an increasing number of pharmaceutical substances, a classification of their environmental hazard and an environmental risk assessment was carried out by Stockholm County Council ⁽⁴⁾. For some substances environmental risks were detected, for others, including most metabolites, gaps of knowledge still exist.

To date, two cases have been identified of **pharmaceuticals affecting wildlife**:

- many countries report that the oestrogen derivate ethinyl estradiol is responsible for the feminisation of male fish, most likely in combination with other hormones or hormone-mimicking substances;
- the anti-inflammatory drug diclofenac, used as a veterinary drug, has killed tens of millions of vultures in Asia.

These cases are well documented. But other pharmaceuticals, including antibiotics, endocrines, antiparasitics, antidepressants and anticancer medications, give reason for concern. Various factors can amplify risks or disguise their impact. For example, effects on small organisms and microorganisms may be less obvious due to their size and therefore not reported. Furthermore, pharmaceuticals are often used as mixtures of several active ingredients. Whereas single substances are mostly found in the environment in modest quantities, mixtures may be sufficient to have an environmental impact. Assessments of individual substances may therefore be misleading.

Following an increase during the last decades, in recent years, total **European sales of pharmaceuticals** remained roughly constant, with a slight decline in 2008. Due to the expiry of patents on important pharmaceutical substances, the occurrence of these substances in the environment may increase. The European antibiotics market grew slightly in the period 2006–2008, whereas the hormone market declined and recovered modestly in the same period. Recent decades have also seen an increase in pharmaceutical substances containing fluorine, which are characterised by improved bioavailability in the human body and greater persistence in the environment.

The environmental footprint of pharmaceuticals can be reduced by various means

Green pharmacy is the design of pharmaceutical products and processes that eliminate or reduce the use and generation of hazardous substances. Following these principles, pharmaceuticals can be generated with reduced impact on the environment during production or after use. The introduction of such processes and pharmaceuticals is currently not a high priority for the pharmaceutical industry but future generations of pharmaceuticals will probably leave fewer residues in the environment.

Because producers, doctors, pharmacists and patients still know little about the environmental effects, fate and behaviour of pharmaceuticals, **communication** on these matters is crucial. The environmental issues can be introduced in already existing information schemes to increase awareness that, in addition to the desired health effects, certain pharmaceuticals may have significant environmental impacts.

All over Europe **wastewater and rivers** contain a broad variety of pharmaceutical substances and their metabolites. Not all of them are known. As the substances occur mainly as the result of medical treatments and can hardly be replaced, pollution is unavoidable and must be addressed through

wastewater treatment. Various treatment methods to purify drinking water are required. Modern methods like UV treatment or advanced oxidation processes are available to reduce pharmaceutical residues.

A considerable amount of unused pharmaceutical products is discharged through the sinks or as household **waste**. Although most European States provide special collection systems, the amounts collected differ widely. This may be partly due to uncertainties or lack of public awareness about environmentally safe disposal.

⁽⁴⁾ Stockholm County Council, 2009. Environmentally classified pharmaceuticals. Available at: http://www.janusinfo.org/imcms/servlet/GetDoc?meta_id=10205 [Accessed 10 June 2009].

Key findings

As a result of the workshop the participants drew up the following proposals for action:

Acceptable environmental impact

- environmental quality standards for pharmaceuticals should be defined;
- environmental risk assessment of human pharmaceuticals should be part of the risk-benefit analysis within the authorisation process, with acceptable residues depending on the therapeutic importance of the pharmaceutical;
- concerning the assessment of the effects of the pharmaceuticals in the environment, the experience with biocides, plant protection products or industrial chemicals on eco-evaluation should be taken into consideration;
- possible risk mitigation measures should be developed as part of the authorisation process.

Eco-classification

- all pharmaceuticals should be classified according to their environmental hazardousness (such system was published by the Stockholm County Council).

Green pharmacy

- incentives for green pharmacy should be considered, such as prolonging patents or lowering costs for less eco-testing by defining waiving criteria for greener pharmaceuticals;
- research in the EU should be initiated including better methods for eco-efficient synthesis, developing new 'greener' pharmaceuticals that break down after use.

Pharmaceutical waste in households

- take back scheme rules for unused pharmaceuticals should be harmonised in the EU, take back should always be carried out by pharmacies and pharmaceuticals should be labelled with 'return unused medication to a pharmacy';
- pharmaceutical waste should always be incinerated;
- informing citizens on take back schemes should include modern information media such as internet and television.

Wastewater treatment

- to destroy unavoidable remnants of active substances and metabolites (mainly from treatment), improved wastewater treatment should be considered, for example using activated carbon, advanced oxidation or UV.

Data availability and evaluation

- more data are required to describe the effects — in particular long-term — and fate of pharmaceuticals in the aquatic environment;
- existing not classified data generated by research or authorisation processes should be collected and made publicly available in an EU database;
- prioritization should be given to evaluating pharmaceuticals with potentially severe environmental effects (e.g. antibiotics);
- a substance tailored testing and evaluation should be selected and new endpoints should be added;

- environmental effects should be included in the 'pharmacovigilance' concept (relating to understanding and preventing adverse effects);
- environmental risk assessment of human pharmaceuticals should also take into account the presence of other substances in the receiving environment with a similar mode of action;
- post-marketing environmental monitoring is needed for surface, ground and drinking water, and for biota;
- data on sewage treatment sludge is required to distinguish between degradation and elimination/removal of pharmaceuticals;
- to improve the eco-classification (see above) and environmental assessment, the responsible environmental authorities should be given access to confidential data gained during authorisation of substances;
- the potential for microbial resistance of pharmaceuticals should be investigated.

1 Sources and differences in use of pharmaceuticals in Europe

Tom Ronnlund
General Manager Nordic & Baltic Region
IMS Health

IMS Health is the world leader in business intelligence and consulting services for the pharmaceutical sector. The following findings derive from our evaluations of the pharmaceutical market.

The global pharmaceutical market is still growing, although the growth rate has been declining for some years. In volume terms of therapeutic standard units, Europe (including Russia, Turkey and Ukraine) is the slowest growing region globally, expanding 1.3 % in 2008. In terms of value of sales, growth in 2008 was negative (-0.4 %) for the first time in many years.

Within Europe, France, Germany and the United Kingdom account for 46 % of the market volume

in tonnes of active ingredients, followed by Spain, Russia and Italy.

For two groups of pharmaceuticals, additional details were provided.

Antibiotics: the market volume in tonnes of active ingredients is still growing but the growth rate has declined substantially (from 4.0 % in 2007 to 1.4 % in 2008). Turkey, France and Russia have the highest antibiotics consumption, followed by Italy, Spain, Germany and the United Kingdom.

Hormones (sexual and other hormones): the market described in International Units of hormone effect has been shrinking since 2006, although the rate of contraction has slowed. In 2008 the market declined by 4 %, compared to - 10 % in the preceding year. Greece, Turkey and Spain consumed more than 50 % of the marketed hormones, followed by Italy, France and the Ukraine.

2 Veterinary medicines in the environment – special emphasis on the fate and transport of antibiotics and antiparacetics with manure and biosolids

Bent Halling-Sørensen, Kristine Krogh and Martin Hansen
Section of Environmental Chemistry
Dept. of Pharmacy and Analytical Chemistry
Pharmaceutical Faculty
Copenhagen Universitet
Universitetsparken 2
2100 Copenhagen Ø
Denmark
bhs@farma.ku.dk

Veterinary medicines (VETmeds) primarily enter the terrestrial environment via different types of manure, slurries or other types of biosolids (Halling-Sørensen *et al.*, 1998; Jørgensen and Halling-Sørensen, 2000). Manure, slurry and biosolids vary markedly in water content and constituents and therefore the resulting VETmed concentration can be quite different.

When wastes are applied to the land it is assumed that the waste components will move through the soil matrix slowly and therefore pathogens will remain in the soil a long time and will die from starvation, scavenging and cold, organic components will be digested by microbes and inorganic components will be adsorbed or taken up by crops or consumed by microbes. These are assumptions are clearly not always true because VETmeds are sometimes identified in the environment.

Why are we concerned?

- more biosolids may be applied than the land can handle,
- the VETmeds and the human medicines contribute to surface and groundwater contamination;
- detectable presence of VETmeds, human pharmaceuticals and resistance determinants in groundwater,
- Increased nutrient runoff into surface waters.

The publications (below) give recent results and furthermore give an overview of results obtained at laboratory scales, semi-field studies and full scale field studies in Denmark. The level of VETmeds concentration levels in manure and slurry is shown, different exposure scenarios for VETmeds are discussed. Compounds to prioritize, such as antibiotics, antiparacetics, due to their fate are emphasized.

2.1 Current state of the problem

VETmeds are designed to be biologically active molecules. The different compound groups are used in large quantities in Denmark (5.2 m inhabitants), often more than 1–10 tonnes/year per year. Scant and often insufficient information is available to perform Environmental Risk Assessment (ERA) of most existing VETmeds. Current ERA methods for drugs have only been in operation for a short time. At present, the only VETmed for which complete information will be publicly available is ivermectin, which is being researched in the context of the 6th Framework's ERApharm project.

2.2 Conclusions

The present state of VETmeds in the environment can be summarised as follows:

- there is limited knowledge on the usage of **certain** VETmeds;
- there is limited knowledge on the fate of **many** VETmeds;
- there is limited knowledge on the ecological effects of **most** VETmed;
- VETmed are often mobile and found in drainage waters;
- there is limited knowledge on biodegradation in manure and slurry;

- more knowledge is needed to predict dissipation/biodegradation in manure/soil mixtures;
- priority compounds are certain antibiotics, ivermectins, steroid hormones;
- antibiotic resistance in the environment needs more attention!

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3 Current known effect of pharmaceuticals

John P. Sumpter
Institute for the Environment
Brunel University
The United Kingdom

There are presently two well documented examples of pharmaceuticals adversely affecting wildlife: ethinyl estradiol (EE2) contributing to the feminisation of male fish, and diclofenac killing vultures.

EE2 plays a role in the feminisation of male fish that has been reported from many countries across the world. The effects reported (elevated plasma vitellogenin concentrations, oocytes in testes and disrupted reproductive ducts) are probably a consequence of exposure to a mixture of estrogenic chemicals, with EE2 being a major component of the mixture in many countries. Laboratory experiments have convincingly shown that EE2 is very potent in fish. Concentrations as low as a few ng/litre feminise males, leading to reduced or no reproduction and population crashes. Even EE2 concentrations below 1 ng/litre have been reported to affect fish. Fish appear to be the most sensitive group of aquatic organisms; it is unclear whether or not low concentrations of EE2 also affect invertebrates.

Diclofenac, used as a veterinary pharmaceutical, has killed tens of millions of vultures in Asia. The drug is administered to ill livestock (especially cows), which are left in the environment when they die to be consumed by scavengers such as vultures. In the last 15 years, three species of vultures have

declined by more than 97 % and are now classified as critically endangered. Diclofenac causes acute renal failure and the vulture dies within a few days. Experimental evidence has confirmed that diclofenac is the cause of this mass poisoning of wildlife. Other non-steroidal anti-inflammatory drugs (NSAIDs) also appear to be highly toxic to birds, including groups other than raptors (to which vultures belong). However, one NSAID, meloxicam, is apparently not toxic to birds. Further better news is that New World vultures are tolerant of diclofenac.

The 'diclofenac killing vulture s' saga demonstrates many important lessons. Pharmaceuticals can reach the environment via unexpected routes (in this case in animal carcasses). Some groups of chemicals may be particularly sensitive to a particular pharmaceutical. We obviously have a lot to learn presently about protecting wildlife from pharmaceuticals.

It is unclear presently whether these two examples will prove atypical and perhaps the only examples of pharmaceuticals adversely affecting wildlife, or whether many more examples will be discovered. A number of preliminary reports (as yet unconfirmed) suggest that low concentrations of other human and veterinary pharmaceuticals can adversely affect a variety of organisms, both vertebrates (e.g. fish) and invertebrates (e.g. snails). A lot more research and often better research is required before it will be possible to judge how serious a threat pharmaceuticals pose to wildlife.

4 Predictive hazard and risk assessment of pharmaceutical mixtures – possible generalisations and open gaps

Thomas Backhaus
Dep. of Plant and Environmental Sciences
University of Gothenburg
Sweden
thomas.backhaus@dpes.gu.se

Although in specific cases even individual pharmaceuticals have been proven to cause environmental harm, the concentrations of individual pharmaceuticals found in European environments are often too low to provoke direct ecotoxicological effects. However, a whole range of different pharmaceuticals is present in a given environmental compartment at any given time. Hence the typical exposure situation in the environment is normally a multi-component mixture of low-effect concentrations of individual pharmaceuticals.

Two classical mixture toxicity concepts, 'Concentration Addition' and 'Independent Action', have been successfully applied to a range of pharmaceutical mixtures. Their power for predicting the joint action of pharmaceuticals is usually good to excellent. Cases of synergistic or antagonistic mixture toxicities (a higher or lower toxicity than expected) are rare.

Because the overall toxicity of a pharmaceutical mixture is in general substantially higher than the toxicity of each individual substance at its concentration present in the mixture (see Figure 4 of this report in Annex), there is a clear need to adequately consider the joint action of pharmaceuticals in their environmental hazard and risk assessment. Concentration Addition and Independent Action might provide valuable instruments for this purpose.

However, several knowledge gaps remain:

- Should we – as a general rule – expect mixtures of dissimilar pharmaceuticals to be toxic even if the individual substances are present at only low, non-toxic concentrations? That this might be the case has been proven once but we lack evidence for populations of multi-cellular organisms and levels of higher biological complexity (communities, ecosystems).
- In almost all ecotoxicological studies of pharmaceutical mixtures in the literature, Concentration Addition predicted a slightly higher mixture toxicity than Independent Action. However, in a few situations the opposite was observed. In particular, the relationship between the two predictions in environmentally realistic settings is still unknown. Can we apply CA as a general reasonable worst case assumption for the predictive assessment of pharmaceutical mixtures? How big an error would we make on average by doing so?
- How often do which confounders have an impact on the predictability? We are especially lacking systematic knowledge on which situations might lead to synergistic effects and which to antagonistic ones.

In addition to these scientific gaps, a major challenge lies in developing strategies on adequately reflecting the joint action of pharmaceuticals in environmental regulation, as current regulatory approaches and frameworks are largely based on the classical substance-by-substance approach.

5 Environmental risk assessment of pharmaceuticals – experiences and perspectives

Anette Küster
Federal Environment Agency – UBA
Pharmaceuticals
Wörlitzer Platz 1
06813 Dessau
Germany
anette.kuester@uba.de

Since 1993 the potential environmental risk of veterinary and human pharmaceuticals has to be assessed before marketing. According to the relevant guidelines (EMEA, 2006, 2007), the Environmental Risk Assessment (ERA) is a tiered process in which the first phase (Phase I) is limited on the intended use considering only environmental exposure. If the predicted environmental concentration (PEC) of a pharmaceutical exceeds a defined threshold value or environmental concerns such as effects on reproduction are apparent, studies on environmental fate and effects have to be performed in Phase II.

The second phase (Phase II) is a hazard quotient approach, comparing the predicted environmental concentration (PEC) with the predicted no effect concentration (PNEC) for various compartments. The marketing authorisation of a medicinal product for human use may not be refused because of environmental concerns. In contrast, for veterinary medicinal products the ERA is part of the risk-benefit analysis and hence the marketing authorisation may be refused due to environmental risk or risk mitigation measures have to be taken.

Results of data obtained from the ERA of pharmaceuticals showed that 95 % of the applied pharmaceuticals were not readily biodegradable according to OECD Test 301. Of the human pharmaceuticals assessed, 15 % were persistent in water and 50 % in sediment (OECD 308, persistence criteria according to EU-TGD). About 50 % of the applied veterinary pharmaceuticals fulfilled persistence criteria for soil (OECD 307).

Eco-toxicity data showed a severe shift of the most sensitive test species used in acute and long-term toxicity data. Whereas for the tested pharmaceuticals in 67 % algae turned out to be the most sensitive

species in acute tests, fish represented the most sensitive species in long-term tests (56 % of the tested pharmaceuticals). Those results underline the necessity of using long-term eco-toxicity tests in the ERA of pharmaceuticals.

For human pharmaceutical products with the standard base set of eco-toxicity tests (fish, daphnia, algae) available, long-term toxicity data (NOECs) were shown to be below 1 µg/litre for a number of applications. A risk for the environment was characterised for human pharmaceuticals with hormone, antibiotic and psychotropic indication. The risk characterisation of veterinary pharmaceuticals showed an environmental risk for nearly all applications with antibiotic and antiparasitic indication. As examples, the results of the ERA for the antidepressant fluoxetine (obtained via the EU project ERA Pharm), the analgesic ibuprofen and the veterinary coccidiostatic toltrazuril were shown to present a risk to the environment.

In conclusion, the ERA of pharmaceuticals is now established for human and veterinary pharmaceuticals and results of the ERA of pharmaceuticals will be available in increasing numbers. Data available up to now confirm an environmental risk for both human and veterinary pharmaceuticals. Further on, eco-toxicity data for pharmaceuticals have been proven to be in the range of measured environmental concentrations.

As a federal environment agency, UBA defines a need of action in the field of guideline development, the development of possible risk mitigation measurements for human pharmaceuticals, and ERA as part of the risk-benefit analysis for human pharmaceuticals. In order to establish post-marketing control mechanisms, monitoring programmes for surface, ground and drinking water and biota on pharmaceuticals with potential risk e.g. PBT are needed. Water quality standards for pharmaceuticals should be determined and a database collecting all ERA results, and effect and fate data (EU projects) should be established in order to identify pharmaceuticals of environmental concern and the scope of remedial actions.

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European Union Technical Guidance Documents in support of the risk assessment of new and existing chemicals and Biocides, <http://ecb.jrc.ec.europa.eu/tgd/>.

OECD Guidelines, Test 301 'Screening of chemicals for ready biodegradability in an aerobic aqueous medium' Source OECD.

OECD Guidelines, Test 307 'Aerobic and anaerobic Transformation in Soil' Source OECD.

OECD Guidelines, Test 308, 'Aerobic and anaerobic Transformation in aquatic sediment systems' Source OECD.

6 Summary of KNAPPE: the known, the unknown, and options for improvements

Benoit Roig
Head of Biodiagnostic and Metrology
department
Ecole des Mines d'Alès, Alès
France
benoit.roig@ema.fr

The Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters (KNAPPE) project is a Sixth Framework Programme Specific Support Action (SSA) project, financed by the European Commission's Research Directorate-General. It aims to establish state of the art knowledge on pharmaceutical products in the environment and to propose recommendations (priority actions) to lower their presence.

Over the duration (18 months) of the project, data concerning manufacture, consumption, occurrence, elimination, impact, regulation and stewardship of pharmaceutical products have been collected and integrated. The findings reveal no evidence that current concentrations of pharmaceutical products in the environment will result in significant environmental impact or human harm. However, there is a public concern that such residues exist and cost-effective measures should be considered to reduce these residues without inhibiting patient care.

KNAPPE discussions have been valuable as a forum for open and honest exchange of views by the stakeholders who have participated in the project and those who have taken part in the meetings. Participants are committed to continuing the dialogue to reach a better common understanding of the issue and have robust answers to future questions on this topic.

At this stage the KNAPPE project has produced some recommendations to reduce the presence of pharmaceutical products in the environment and hence mitigate the general public's fears. They focus on two main areas:

1. Advancing scientific and technical knowledge concerning the fate and effect of pharmaceutical products.

Specific actions in this area include:

- *reviewing the effectiveness of current and potential sewage treatment plant (STP) processes for removing pharmaceutical products* — the efficiency of wastewater and drinking water treatment processes needs to be improved, either by optimising existing systems or introducing improved technologies;
- *increasing knowledge of the environmental effects of pharmaceutical products* — 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;
- *developing intelligent testing strategies for chronic toxicity assessment* — intelligent testing strategies need to be developed to improve the assessment of chronic toxicity; this should include assessments of mode of action and utilise emerging data from 'omics' technologies.
- *further investigate the fate of pharmaceutical products in sewage treatment plants* — the interaction between pharmaceutical products and solids, particularly in wastewater treatment plants needs further study, particularly the issue of whether residues are permanently bound to solids or if they can be released back into the environment;
- *evaluating the role of environmental monitoring in risk assessment* — there is a need to improve monitoring strategies; a priority list of pharmaceutical products 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;

- *evaluating the practicalities of adopting 'green pharmacy'* — the development of 'greener' pharmaceuticals needs to be stimulated by providing the incentive of increased patent life or incorporating the outcome of environmental risk assessment into the drug approval process.
- ### 2. Controlling emissions of pharmaceutical products into the environment.

Specific actions in this area include:

- *evaluating the effectiveness of classification schemes* — the Swedish system for environmental classification of pharmaceuticals is a good method for providing information to health professionals and patients, and its value and benefits are currently being reviewed. It is recommended developing a general European framework for environmental classification, which could be adapted from country to country to reflect the specific medical practices and drug consumption in each;
- *unused medicines management* — 'take back' schemes for unused medicines represent

one of the simplest ways to reduce inputs of pharmaceutical products to the environment. It is recommended gathering quantitative information on the efficiency of existing schemes so that each Member State can adopt best practices, including regarding providing information to patients. A European guideline could be very useful;

- *evaluating methodologies to better inform the 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;
- *evaluating the need for policy framework reform* — the current policy framework is considered sufficient to deal with the issue of pharmaceutical products in the water environment although implementation could be improved e.g. using take back schemes. Environmental risk assessment procedures need to be kept up to date and should be applied to existing, as well as new medicines. The upgrading of wastewater treatment systems might be an option to reduce environmental residues further but this need to be considered in the light of costs (both financial and environmental), risks and benefits.

7 Status and potential of 'green pharmacy'

Prof. Dr. Klaus Kümmerer
Department of Environmental Health Sciences
Freiburg University Medical Center
Breisacherstraße 115 b
79106 Freiburg
Germany
Klaus.Kuemmerer@uniklinik-freiburg.de

Green pharmacy is the design of pharmaceutical products and processes that eliminate or reduce the use and generation of hazardous substances along the whole life cycle. This includes preventing environmental or health and safety impacts at source; reducing impacts is merely a short- to mid-term alternative. There is a high degree of interconnectedness of sustainable chemistry and sustainable pharmacy.

Green and sustainable pharmacy is an emerging topic. Its environmental, social and economical potential is high. However, it is not yet fully understood and is at early stages of implementation. According to the principle of sustainability and the principles of green chemistry, the whole life cycle of a compound has to be considered to identify opportunities to manage and reduce risk. That means taking into account elements such as design of compounds, use of raw materials, synthesis, manufacturing, use and life after excretion and/or disposal.

For the petroleum-based raw materials and renewable feedstock, the issues are the same general ones as in the chemistry and energy sectors (e.g. shortages and prices). They are, however, probably of lower significance for pharmaceutical industries. Because of the focus on the whole life cycle; raw materials are the very first station. However, the substance flows are smaller. New platform molecules from bio-refineries will come up, an option intensively studied for green chemistry. This may be a bigger challenge for green pharmacy. However, pharmacy has a long lasting tradition in using natural compounds.

Another issue is the patenting of organisms. There are the same general problems as in chemistry and in the energy sector with the application and acceptance of genetically modified organisms and patents on nature's organisms.

The environmental impact of manufacturing 1 kg of product in the pharmaceuticals sector is very much higher than in chemical industries (Shelden, 2007). However, the biggest progress within greening pharmacy has been made in this field. Innovations include less hazardous solvents, new synthesis routes, application of different reactors, intensified use of (bio) catalysis and biosynthesis, new methods of separation and extraction improved yield and decreased waste and wastewater. As technical progress in this field impacts revenues directly by reducing costs for materials, energy and waste, pharmaceutical companies have focused most efforts at this stage of a pharmaceutical's life cycle.

Emissions from manufacturing of pharmaceuticals are assumed to be low in Europe and the USA. There may, however, be exceptions from this general rule (Thomas *et al.*, 2008). In other countries emissions may be very high and would not meet standards set in Europe or the USA (Larsson *et al.*, 2007; Li *et al.*, 2008). Improvements are possible with regard to packaging material and package size.

For the use and after use phases, three different approaches are possible to reduce the input of pharmaceuticals into the aquatic environment (Kümmerer, 2007):

1. Advanced effluent treatment is still the approach that is favoured despite its increasingly visible technical and economical limitations and unsatisfactory performance (Kümmerer, 2008). This approach is probably not sustainable (Jones *et al.*, 2007; Wenzel *et al.*, 2008).
2. For the use of pharmaceuticals, informing and educating medical doctors, pharmacists and patients is necessary. A good example is the Swedish system (Gunnarson and Wennmalm, 2008). However, handling pharmaceutical waste and outdated medicaments properly and reducing their use is not enough (Castenson, 2008). Systems for returning outdated medicaments are in place in several countries and should be according to EU legislation, however in everyday practice there are still many shortcomings (see speech G. Vollmer).
3. A promising long-term approach is the rational design of new pharmaceuticals ('benign by

design' according to Kümmerer, 2007). Figure 3 of this report shows an example. Such design addresses not only pharmaceutical properties for new medications but also environmental aspects such as improved degradation or elimination through conventional effluent treatment from the very beginning (Daughton, 2003; Kümmerer, 2007; Boethling *et al.*, 2007). The next steps should be to set up research and education programmes, to create and to identify success stories and to identify opportunities and limitations (Schramm and Kümmerer, 2008; www.start-project.de) of this new and sustainable approach.

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8 The pharmaceutical sector – driving change in relation to pharmaceuticals in the environment

David Taylor
Strategic Director
wca environment
david.taylor@wca-environment.com

The development of 'green' pharmaceuticals is currently not a high priority for the pharmaceutical industry. To be successful, any attempts to change this need to understand the context in which the industry operates and to consider the most effective drivers to elicit the required behaviour.

The pharmaceutical sector consists of two major groupings; a high risk/high profit innovation sector and a low risk/low profit generic manufacturing sector. The innovation companies, although research based, are in fact predominantly development and marketing organisations in which the key decisions on drug development are commercially based rather than scientific.

Over the next five years most of the major innovation companies are facing dramatic reductions in their income, resulting from a series of patent expiries. This has coincided with a continuing significant fall in innovation, despite the major increase in research effort. At the same time regulatory requirements are increasing the duration and cost of development whilst

pharmaceutical pricing is under pressure from health providers and governments.

In response the industry is trying to reduce development times (to extend available patent life) and to increase the success rate in development. Both of these produce a more risk averse approach where any potentially negative consequence lead to early termination of development. Thus any mechanism intended to promote greener pharmaceuticals by imposing costs or constraints on 'non-green' products would probably lead to a further reduction in innovation.

The alternative approach of providing a marketing advantage for green pharmaceuticals via some additional market exclusivity would be much more likely to stimulate a behavioural change, just as it did with the orphan drug initiative.

Environmental residues left by the current generation of pharmaceuticals are already very low and even without additional regulatory intervention the next generation of pharmaceuticals will produce lower environmental residues. Advances in personalised medicine and the rapid expansion of the biopharmaceuticals area will all contribute to major reductions in environmental residues.

9 The potential for better communication between doctors, pharmacists and patients

Åke Wennmalm
Environmental Director
Stockholm County Council
Sweden
ake.wennmalm@sll.se

Communicating the environmental effects of pharmaceuticals to key organisations and persons is important to achieve the better routines and management needed to avoid emitting pharmaceutical residues into the environment. The following lines will briefly describe how Stockholm County Council (SCC), in close collaboration with Apoteket AB (AAB, owner of all pharmacy shops in Sweden), approaches this communication issue.

A number of operational levels for communication have been identified, comprising EU and government authorities, pharmaceutical producers, those responsible for prescribing medication and other health care staff, pharmacological committees, patients and water authorities.

Earlier, attempts to improve the EU legislation for human medicines consisted of successful lobbying that yielded considerable improvements of the environmental aspects of current legislation (2004/27/EC). In December 2008 the European Commission launched a 'pharma package' communicating a new strategy for the pharmaceutical legislation, as well as proposals for changes to Directive 2001/83/EC with respect to information to patients, pharmacovigilance and counterfeit medicines. SCC and AAB presently consider proposing some amendments to these proposals.

The most important such amendment would be to extend the pharmacovigilance concept to include not only public health and patient health but also the environment. This would create a platform for improved environmental protection in the proposal. In parallel it seems necessary to extend the current definition of 'risk-benefit balance' to comprise also the environmental impact of medicines on the risk side. It also seems urgent to clarify and stress the importance of the present legislation's requirement of recollection systems for unused or expired medicines. Such recollection systems were required already in the 2004 review of Directive 2001/83/EC but that requirement has not received sufficient attention in several member countries.

Communication with producers has yielded a joint project in Sweden between health care stakeholders and pharmaceutical producers resulting in a system for classification of environmental risk and hazard of human medicines. The system is operated by the producers under surveillance of an independent party and has hitherto produced risk and hazard classification of about 420 pharmaceutical substances (amounting to about 70 % of the pharmaceutical sales in Sweden, see also Figure 2 of this report). This classification is presented openly (www.fass.se) and in three different levels (directed to patients, prescribers, and experts like pharmacological committees). SCC produces an annual printed version of the classification to enhance use of the data for prescribers, other health care staff, patients and water authorities. A web-based version is also available (www.janusinfo.se).

10 Pharmaceuticals as waste in households

Gerald Vollmer
European Environment Agency
Copenhagen
Denmark
gerald.vollmer@eea.europa.eu

To improve knowledge on amounts and routes of pharmaceutical waste within Europe, a questionnaire was sent via the European Environment Agency (EEA) national focal points to all EU authorities responsible for this type of waste. The questionnaire was also sent to Albania, Croatia Iceland, Lichtenstein, Norway, Serbia and Switzerland. In total, 28 states replied. Due to the limited importance of pharmaceutical waste in hospitals and their different ways of disposal, this survey covered pharmaceutical products as waste in households only.

The questions focused on:

- how information is given to the citizen on best way of disposal of unused pharmaceuticals in households;
- whether pharmaceutical waste is classified as normal household waste or special waste;
- who collects pharmaceutical waste (special waste);
- whether there is a legal obligation to participate;
- an estimation of annual amounts.

A broad variety in information policy was detected. The information channels range from providing direct oral information to the patient by doctor or pharmacist on the best way of disposal

to comprehensive information via websites, brochures, information on collection containers and information on the package of the pharmaceutical product. In Belgium, Spain and Sweden all of those routes of information provision apply.

Besides Malta, Serbia and North Rhine Westphalia, all States and regions classify pharmaceutical waste as special waste. (see Figure 1 of this report in Annex) This 'non-household' waste is – beside Slovenia – to be returned to a pharmacy. In eight States it can be also given to a public waste collection point.

There is no harmonised rule on whether the pharmacies participate because of legal obligation or on voluntary base. In most states it is on voluntary base.

The amounts of collected pharmaceutical waste differ widely: from 0.19 tonnes/million capita in Croatia to 237 tonnes/million capita in Switzerland. Most of the states reported or estimated the amount of collected pharmaceutical waste between 10 and 100 tonnes/million capita. Taking into consideration the number of pharmaceutical packages distributed, there is a broad variety in collection behaviour. The return rate in Switzerland is very high, followed by Ireland, Luxembourg, Sweden and France. In the majority of the states, a recovery scheme is established.

Other surveys carried out during recent year's show that a considerable amount of unused pharmaceuticals are not returned to the pharmacy. An important part of the unused pharmaceuticals – specifically liquid pharmaceuticals like drops and syrups – are discharged via the sink or toilet. It is difficult to estimate this amount. As an average of all states, probably 50 % of the unused packages are not collected via a pharmacy.

11 Advanced sewage treatment – technical and economical feasibility

Anna Ledin, Henrik R Andersen and Jes la Cour Jansen
Technical University of Denmark and Lund University
anl@env.dtu.dk

Modern wastewater treatment systems are built for collection and transportation of wastewater. They also aim to reduce organic matter, which may cause oxygen depletion in receiving surface water, and reduce nutrients (nitrogen and phosphorus) that can cause over-fertilisation of receiving lakes, streams and the sea. When pharmaceuticals and their remains after use enter the wastewater system they follow the water and enter the wastewater treatment plants where their fate is governed by their physical, chemical and biological properties. The pharmaceuticals can, in some cases, be biologically degraded if the process conditions are favourable in the plant. They can also be moved from the water phase to sewage sludge due to sorption or to the air by stripping. At present, knowledge is rather weak regarding practical experience on removing and degrading pharmaceuticals at wastewater treatment plants.

The search for more effective treatments (in technical and economic terms) is a question of finding solutions that match the most environmentally significant pharmaceuticals, quantifying their reduction in existing treatment plants and then using promising new treatment methods that can be combined with existing ones to secure the necessary removal. A number of different new treatment technologies needs to be evaluated because the most environmentally significant pharmaceuticals have not been identified yet. In addition it is anticipated that various different substances with rather different chemical properties will be identified among those that need removing.

As treatment must take place at existing facilities with very different processes and capacity to remove pharmaceuticals today, the methods needs to be tailor-made to almost each individual plant or group of plants with similar process schemes.

Among promising physical methods are different kinds of filters (sand filters, disc filters, membrane, micro and ultra filters), which can be used to remove particle-bound pharmaceuticals. Membranes with very small pore sizes such as those used for reverse osmosis, nanofiltration and ultrafiltration can be used for direct removal of some pharmaceuticals. Several types of sorbents (activated carbon, minerals and molecular imprinted polymers) have characteristics that justify evaluating their ability to remove pharmaceuticals.

Among promising chemical methods are advanced oxidation processes (e.g. Vacuum-UV, UV/H₂O₂, H₂O₂/O₃ and UV/O₃) and selective oxidation reagents (ClO₂, MnO₄⁻ and O₃) that can be used to oxidise pharmaceuticals. By this treatment they generally lose the pharmaceutical potency and become more easily biodegradable. Selective reagents can be used for removing a very broad spectrum of pharmaceuticals and advanced oxidation processes might be the solution in cases where a complete oxidation of organic material is necessary to destroy pharmaceuticals that are difficult to remove with other methods.

Improved biological methods can be applied for biological degradation of a broad spectrum of pharmaceuticals. Traditional biological wastewater treatment has been used to partly remove or degrade some pharmaceuticals and degradation may be enhanced by increasing the sludge age in existing biological treatment or by cleaning the effluent in new processes tailor-made for that purpose. A more radical option is to use membrane bioreactors for removal of the pharmaceuticals by extended biodegradation

The mentioned methods for removal or destruction of pharmaceuticals have different added benefits and problems related to the process. Among the most important ones are production of non-wanted transformation products, increased sludge handling, and increased use of chemicals and costs associated with implementation.

List of participants

Chairman

Joop De Knecht, RIVM, Bilthoven, The Netherlands

Speakers

Tom Ronnlund, IMS Health, Espoo, Finland

Bent Halling-Sørensen, Copenhagen Universitet, Copenhagen, Denmark

John P. Sumpter, Brunel University, Uxbridge, the United Kingdom

Thomas Backhaus, Göteborgs Universitet, Göteborg, Sweden

Anette Küster, Umweltbundesamt, Dessau, Germany

Benoit Roig, Ecole des Mines d'Alès, Alès, France

Klaus Kümmerer, Universität Freiburg, Freiburg i. Br., Germany

David Taylor, wca-environment, Faringdon, United Kingdom

Åke Wennmalm, Stockholms läns landsting, Stockholm, Sweden

Gerald Vollmer, European Environment Agency, Copenhagen, Denmark

Anna Ledin, Danmarks Tekniske Universitet, Lyngby, Denmark

Participants

David Gee, European Environment Agency, Copenhagen, Denmark

Dorota Jarosinska, European Environment Agency, Copenhagen, Denmark

Peter Korytar, European Commission, DG Environment, Brussels, Belgium

Peter van Vlaardingen, RIVM, Bilthoven, The Netherlands

Bo N. Jacobsen, Avedoere Wastewater Services, Hvidovre, Denmark

Per Spindler, Københavns Universitet, Copenhagen, Denmark

Annex: figures

Figure 1 shows the ways that pharmaceutical waste in households is classified. The majority of states responding to an EEA questionnaire reported that they require such waste to be collected separately to avoid risks to small children.

Figure 2 illustrates the dangers that pharmaceuticals present to the environment. An assessment of several hundred pharmaceuticals carried out by the Stockholm County Council show a considerable amount of persistent and bio-accumulative substances.

Figure 3 presents an example of the development of a 'green' drug, which is active yet biodegradable after use.

Figure 4 shows that the eco-toxicity of a mixture of pharmaceutical substances is often higher than the sum of the effects of its individual components. A mixture can have considerable eco-toxicity, even if all components are present in concentrations that individually have insignificant eco-toxic effects.

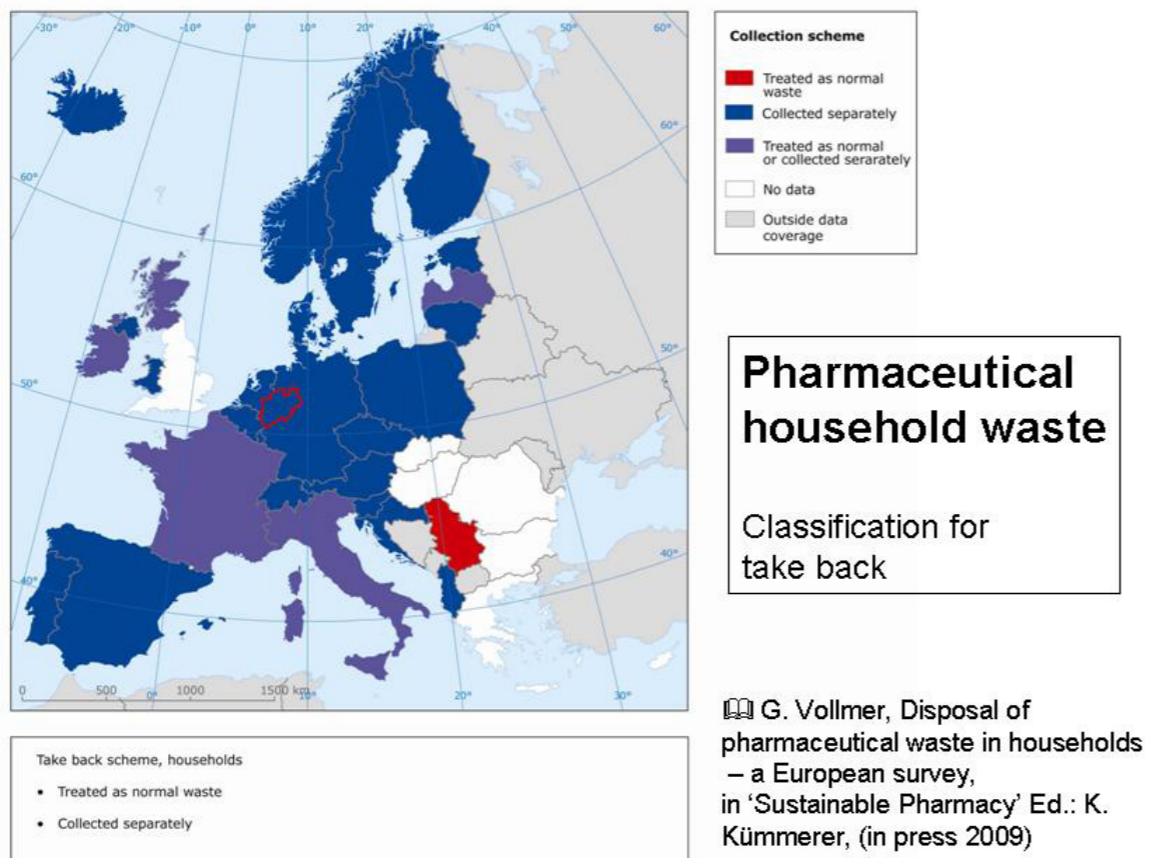


Figure 1

Environmentally classified Pharmaceuticals

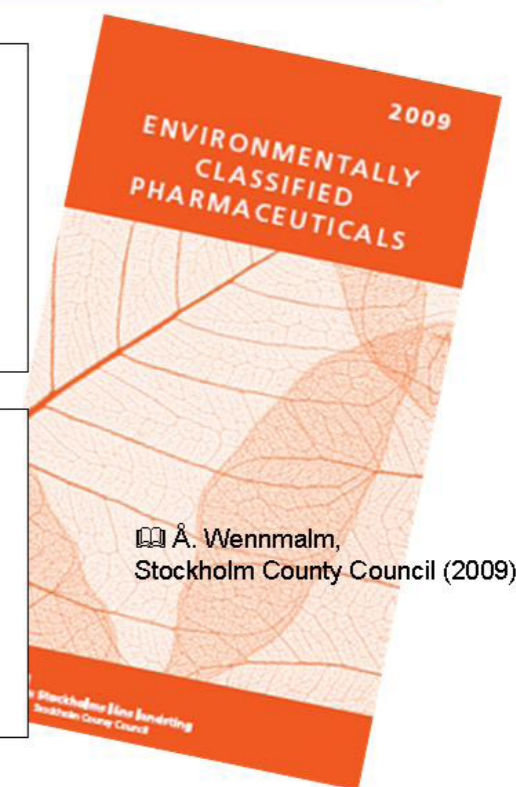
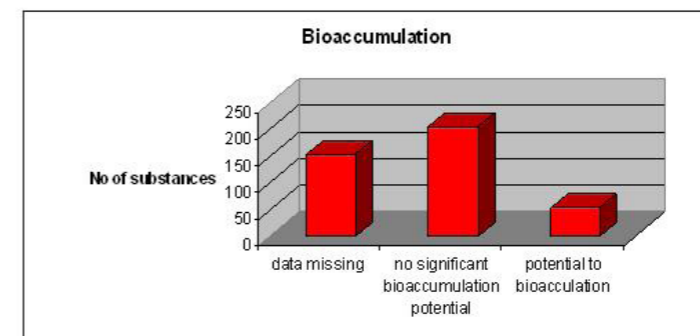
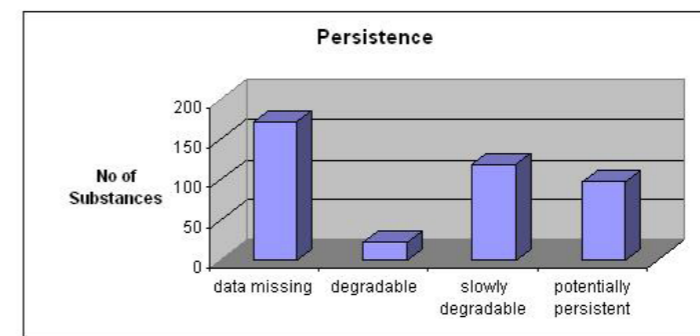
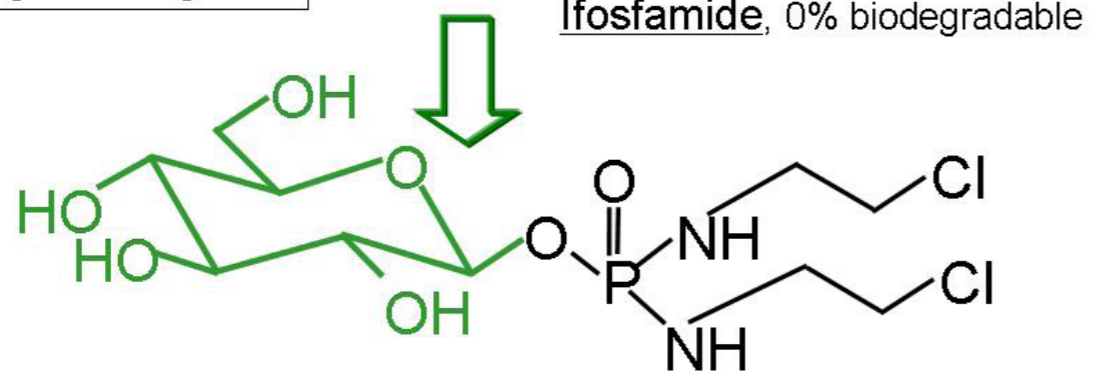
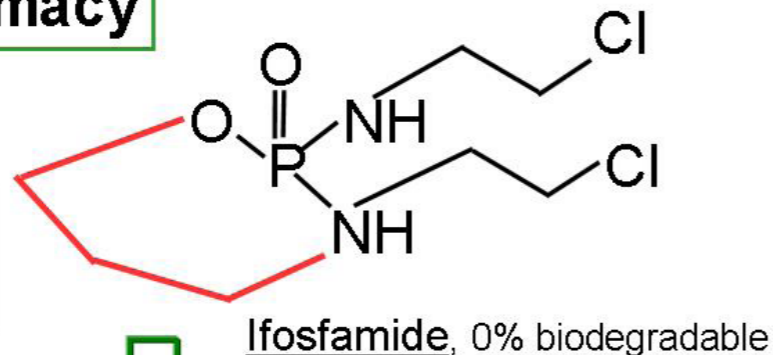


Figure 2

Green Pharmacy

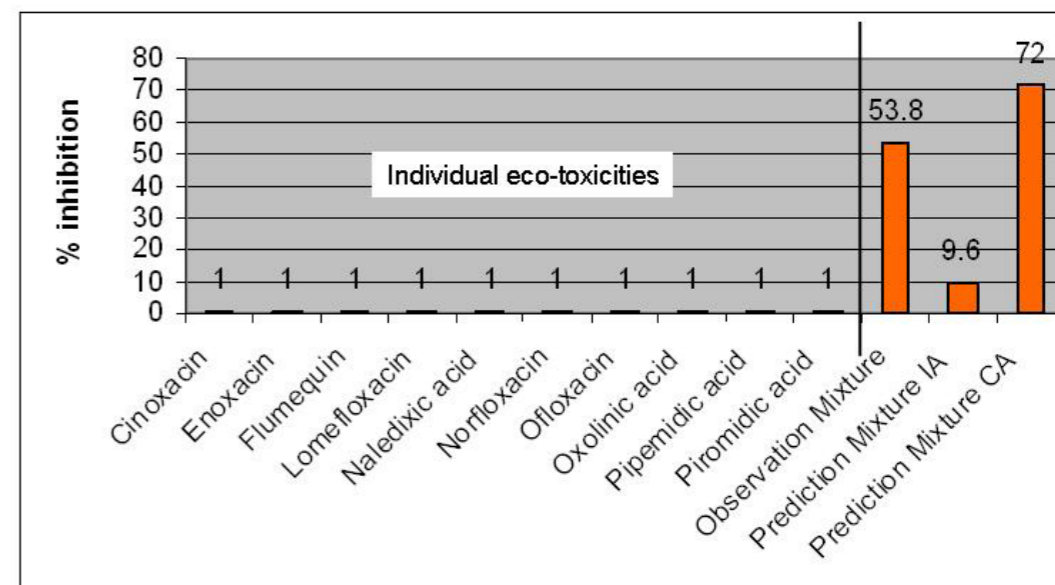
Example for the Development of a "green" drug



Wießler et al. 1998, Kümmerer et al. 2000, Chemosphere, 40, 767, <http://www.thresholdpharm.com/sec/glufosfamide>

Figure 3

Quinolone antibiotics, mixture toxicity



Mixture ratio: EC₀₁ of the components

IA and CA are two concepts used for the prediction of the mixture toxicity.

T. Backhaus, J. Sumpter, H. Blanck, On the ecotoxicity of pharmaceutical Mixtures, in Pharmaceuticals in the Environment (Ed.: K. Kümmerer)

Figure 4

European Environment Agency

Pharmaceuticals in the environment
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European Environment Agency
Kongens Nytorv 6
1050 Copenhagen K
Denmark

Tel.: +45 33 36 71 00
Fax: +45 33 36 71 99

Web: eea.europa.eu
Enquiries: eea.europa.eu/enquiries

