pills
Pharmaceutical Input and Elimination from Local Sources

Pharmaceutical residues in the aquatic system – a challenge for the future

Insights and activities of the European cooperation project PILLS

A European partnership project of:
Emschergenossenschaft (DE), Waterschap Groot Salland (NL),
Centre de Recherche Public Henri Tudor (LU), Eawag (CH), Glasgow
Caledonian University (UK) and Université de Limoges (FR)

EMSCHER GENOSSENSCHAFT
ON BEHALF OF THE PILLS PARTNERSHIP

Investing in Opportunities
This project has received European Regional Development Funding through INTERREG IV B.
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INTERREG IVB

PREFACE AND AUTHORS

This summary is designed to give a brief overview about the work of 6 partner institutions from 6 European countries that have worked together for nearly 5 years on potential solutions concerning the elimination of pharmaceutical residues in waste water. More details can be found in the complete report, available via contacting the partners (see overleaf).

The project's full name "Pharmaceutical Input and Elimination from Local Sources" encompasses the idea of investigating waste water quality and researching and testing elimination methods to achieve better waste water treatment at the source. In this sense the work of the cooperation can be stated to be extremely successful. The increase in understanding of the issue, both in scientific terms and amongst the various communities (political, operational, public) has been dramatic during the last five years and the PILLS project has contributed to this in no small way with around 50 papers, more than 130 articles published reporting about the project and 150.000 visits to the website. We know now that it is possible to eliminate pharmaceuticals at one important point of use, the hospitals, and that it makes sense to do so from an ecotoxicological and multi-resistant bacteria point of view. However, doing so will be expensive and it is not certain this is warranted from a purely environmental or life cycle analysis point of view. Alternative approaches should be investigated and therefore the consortium has proposed a follow up project to study the impact of avoidance and optimisation of biological removal processes.

Four of the six PILLS partners worked together with local partner hospitals on the development of treatment facilities that were designed especially for the treatment of the hospital waste water. The hospitals cooperated voluntarily and the PILLS partners are grateful for their support and assistance – without the commitment of the partner hospitals PILLS would not have been possible.

The PILLS partnership was supported by the Interreg IV B Northwest Europe programme. This EU funding programme offered excellent support by enabling the involved institutions to work together within a wide range of activities. The experts meetings and exchange were funded as well as practical development of treatment facilities with associated research, dissemination and publicity actions and the organization of the partnerships' activities.

Many colleagues supported the work within the partnership and helped to make PILLS a success. We would like to express our thanks to all of them, even if they are not mentioned here by name. On behalf of the involved partner institutions the PILLS final report was written with the support of the following colleagues (in alphabetical order):

- PILLS Partner 1 Emschergenossenschaft: Kirsten Adamczak, Sven Lyko, Issa Nafo
- PILLS Partner 2 Waterschap Groot Salland: Herman Evenblij
- PILLS Partner 3 Centre de Recherche Public Henri Tudor: Alex Cornelissen, Elorri Igos, Kai Klepiszewski, Silvia Venditti
- PILLS Partner 4 Eawag: Lubomira Kovalova, Christa McArdell
- PILLS Partner 5 Glasgow Caledonian University: Karin Helwig, Ole Pahl
- PILLS Partner 6 Université de Limoges: Olivier Barraud, Magali Casellas, Christophe Dagot, Corinne Maftah, Marie-Cécile Ploy, Thibault Stalder

The full report of the PILLS project is attached to the printed version of this summary on a CD.

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BACKGROUND - WHY PILLS ?

We cannot imagine our society without them: highly active modern pharmaceuticals. They help to prevent or cure diseases or make our life more convenient. Large quantities of various pharmaceutically active substances are manufactured today for the protection of humans and animals.

As a result of improved medical care, rising life expectancy and the progressive industrialization of agriculture, an increasing amount of medicinal products are consumed. Today about 3.000 pharmaceutical active substances have permits in Europe. These products are, however, in many cases not completely absorbed and metabolized by the patient but partially excreted. Depending on the specific circumstances, tests of the PILLS partners showed that up to 70 % of the total medicament consumption within a hospital may be excreted or washed off. Therefore traces of the products reach the water cycle.

It is not only the growing use of medicinal products that has led to an increased awareness of this topic however: Thanks to enormous advancements in chemical analysis technologies, many pharmaceutical residues can now be determined in water at extremely low concentrations, often many times lower than was possible several years ago. As a result, concentrations can now often be detected in the nanogram per litre range.

The concentrations of pharmaceutical residues, which are detected in the water, are very low and according to the current state of knowledge are not harmful to humans. However, for many substances it is unclear what effects these residues have on the water habitat – for example on micro organisms. Other micropollutants are already known as harmful for the environment. In these cases politics are asked to react.

The EU published the new draft annex for the Water Framework Directive in Jan. 2012 and if this WFD annex passes the Council and Parliament, all member states' surface waters have to meet the environmental quality standards for the priority substances by 2021 – for the first time including pharmaceutical substances as well. The focus is at the moment on the natural hormone Estradiol and the synthetic hormone Ethinylestradiol contained in contraceptive pills and Diclofenac (a pain killer and anti-inflammatory drug).

How this reduction shall be realized is currently an open question – it may happen by waste water treatment, prohibition of substances or other options.

Regarding the PILLS project one approach to deal with pharmaceutical micropollutants was the investigation of point source treatment:

- Which impact may point source treatment have on the load of specific substances that are mainly consumed in hospitals?
- Which techniques are appropriate to reduce the concentrated discharge at hospitals and care homes?
- What is the effect of this cocktail of pharmaceuticals on the bacteria population in the waste water treatment plants, in terms of the spread of multi-resistant bacteria?

When the relatively large consumption of pharmaceuticals in private households is compared with the much smaller level of consumption in hospitals, it is clear that point sources treatments at the hospitals can only ever be part of the solution. Additional approaches are needed to significantly reduce these micropollutants in the water cycle. However, the PILLS partners were aiming at defining starting points for the elimination and generate the basis for adapted solutions for clearly defined challenges.

River Tweed in Scotland close to Galashields WWTP

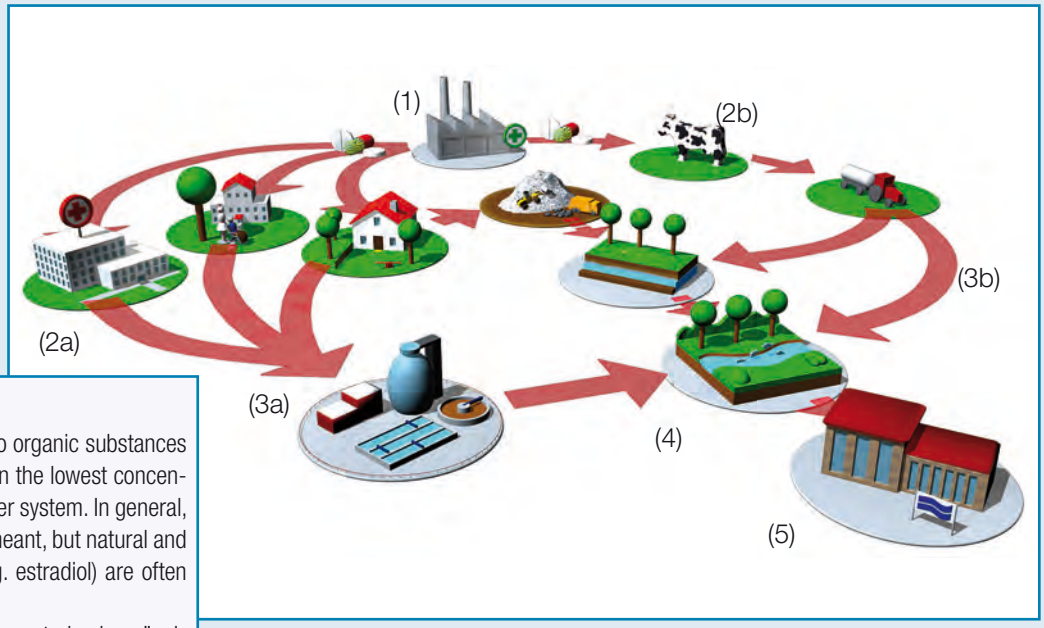


Figure 1: The life-cycle of pharmaceuticals

Micropollutants
"Micropollutants" refers to organic substances or metals that are found in the lowest concentratons (traces) in the water system. In general, synthetic chemicals are meant, but natural and geogenic substances (e.g. estradiol) are often included.
These substances are characterised as "pollutants" if their presence is liable to cause pollution. "Hazardous substances" refers to substances that are toxic (poisonous), persistent (low biodegradability) and liable to bioaccumulate (concentrate within the organism) or to other substances which give rise to an equivalent level of concern.

The life-cycle of pharmaceuticals

Pharmaceutical residues reach the water system by various paths and in order to identify these, the entire life-cycle of pharmaceutical substances needs to be considered.

This life-cycle starts with the development and production of pharmaceuticals (1). Here, during the manufacturing process, waste water may be contaminated by pharmaceuticals. Although this waste water is pre-treated, it is possible that residues are emitted into the water system.

After production, the pharmaceuticals are used in human (2a) or veterinary (2b) medicine. In the case of human medication (2a), active substances may not be completely absorbed by the body; they are partially excreted unchanged and reach the central waste water treatment plants (3a). However, modern waste water treatment methods are not able to completely eliminate most of these substances, since they are primarily designed for the removal of biodegradable substances and nutrients such as phosphorus and nitrogen. Therefore, these residues may pass through the treatment plants and reach surface waters such as rivers and lakes. Further emissions can result from leaks in the sewers, as a result of emergency sewage overflows during heavy rainfall, or come from the sewage sludge when used in agriculture. The consequence of these emissions is that pharmaceutical residues – even in very low concentrations – can be detected in surface waters (4) or in water for drinking water production (5).

Pharmaceutical residues resulting from veterinary use get into the ground and surface water (4), mainly through the deposition of liquid manure on arable land (3b).

At first thought, it might therefore be reasonable to avoid pharmaceutical residues altogether in order to protect our water system. However, not producing and not taking medication does not represent a realistic or desirable scenario. Another option is to take technical measures to clean the burdened water. But a complete elimination of all micropollutants is for practical and economic reasons not reasonable. In this respect life completely without pharmaceutical residues in our industrial society is not achievable. The focus must therefore be on minimisation.

A very promising approach to minimise pharmaceutical residues in the water cycle appears to be one that involves all stakeholders across the entire life-cycle of pharmaceutical substances. Only if all involved parties – from industrial producers to human or veterinary medicine users to waste water management companies and drinking water suppliers – take precautions in their respective fields, can this burden on water systems be effectively reduced.

OBJECTIVES AND WORK CONTENT

Six partners from Northwest Europe – two water boards from Germany and the Netherlands, two research institutions from Switzerland and Luxembourg and two universities from Scotland and France – worked together on the PILLS project. They focussed on the path of human pharmaceuticals and specifically on waste water treatment. Since the concentration of pharmaceutical residues at point sources such as hospitals was considered to be comparatively high, they tested new waste water treatment technologies at these points for the removal of the residues.

To achieve the objectives the project partners devised the following project components:

- Work package 1: Characterisation of the pharmaceutically burdened waste water

  The analysis of the waste water that is contaminated with pharmaceutical residues as well as a characterisation of the waste water flows regarding their chemical quality, ecotoxicological potential and relevance of antibiotic resistance is in the centre of this work package.

- Work package 2: Design, construction and operation of waste water treatment plants at hospital locations which incorporate advanced treatment technologies

  Technologies for the treatment of pharmaceutically burdened waste water are further developed and tested in practice by the construction of two pilot plants and two full scale treatment plants. To this end each partner cooperates with a hospital in their region.

- Work package 3: Assessment of different advanced treatment technologies

  The efficiency (regarding the elimination efficiency of pharmaceuticals and the reduction of ecotoxicological effects and antibiotic resistant bacteria), the costs and the environmental balance (made using a life-cycle assessment methodology) of the advanced treatment technologies is evaluated.

- Work package 4: Communication of the issues and of the results of the project

  Various communication measures enable an exchange of information in the scientific and political field. Furthermore, the topic is brought to the attention of the broader public to make them aware of the issues.

The analytical detection of pharmaceuticals or other micropollutants in concentrations lower than a few nanogram per litre doesn't allow for a conclusion about possible toxic effects of single substances or about the effects of a mixture of compounds on the environment. The toxic effects could involve endocrine disruption, gentoxicity or antibiotic effects. Therefore toxicological tests were used in order to assess the ecological risk of tested water even if the substances are at lower concentrations in the environment. Besides the characterisation of the hospital waste water and the evaluation of the treatment performance regarding the reduction of ecotoxicological effects the tests should also allow the assessment of possibly toxic effects induced by the advanced treatment with ozone or UV (possible effects due to by-products after ozonation or UV-treatment).

Another aspect of growing concern are antibiotic resistant bacteria that are likely to be found in waste water containing antibiotics. Therefore the appearance of antibiotic resistant bacteria in the waste water were investigated in order to find an answer to the question to what extent a hospital is a source for antibiotic resistant bacteria or not. Furthermore, the performance of the advanced treatment techniques to reduce the propagation of antibiotic resistance was assessed.

The partnership is advised by a scientific advisory board, which is associated with the project for its duration. The members of the scientific board come from science, industry and public administrations. It is asked to provide critical feed-back related to the project results and provide information sources as well as ideas based on their individual expertise. Furthermore, the scientific board supports integrating the projects´ findings into discussions at European level.

In Europe there are estimated to be more than 100,000 chemical substances in circulation and, of these, more than 3,000 approved active substances are medicinal products. Amongst this vast array of chemicals it was important that the partnership identified the substances which all partners of the different countries should be analysing in order to obtain comparable results.

For the selection of these key pharmaceutical substances to be analysed, the following three criteria had priority:

- Which active substances are used in hospitals and are also found in the aquatic system?
- Which active substances have known ecotoxicological effects and may therefore represent the greatest risk to the environment?
- Which active substances are not eliminated in the conventional treatment process and must be removed using advanced treatment methods?

As expected it was found that in the investigated hospitals in the different countries, some active substances are found repeatedly – although the concentrations vary from region to region. However, some pharmaceuticals with a high consumption in some partner hospitals were not used at all in others. Based on the above considerations, the partnership selected 16 key substances out of eight substance groups for the project: analgesics, anesthetics, cytostatics, antibacterials, X-ray contrast media, anticonvulsants, lipid regulators and betablockers.

Pharmaceutical consumption and hospital contribution

In the EU, the average number of hospital beds per 10,000 heads of the population varies from 35 (Denmark and Portugal) through to 83 (Germany). Considering the local situation data from Switzerland show that here a ratio of 5-50 hospital beds per 1,000 inhabitants ist connected to the municipal waste water treatment plants.

Figure 2 shows the range of predicted pharmaceutical loads per bed, based on annual dispensed amounts. For comparison the maximum annual amounts of the selected pharmaceuticals dispensed in the community for the UK Borders region was < 2 gram per head of population.

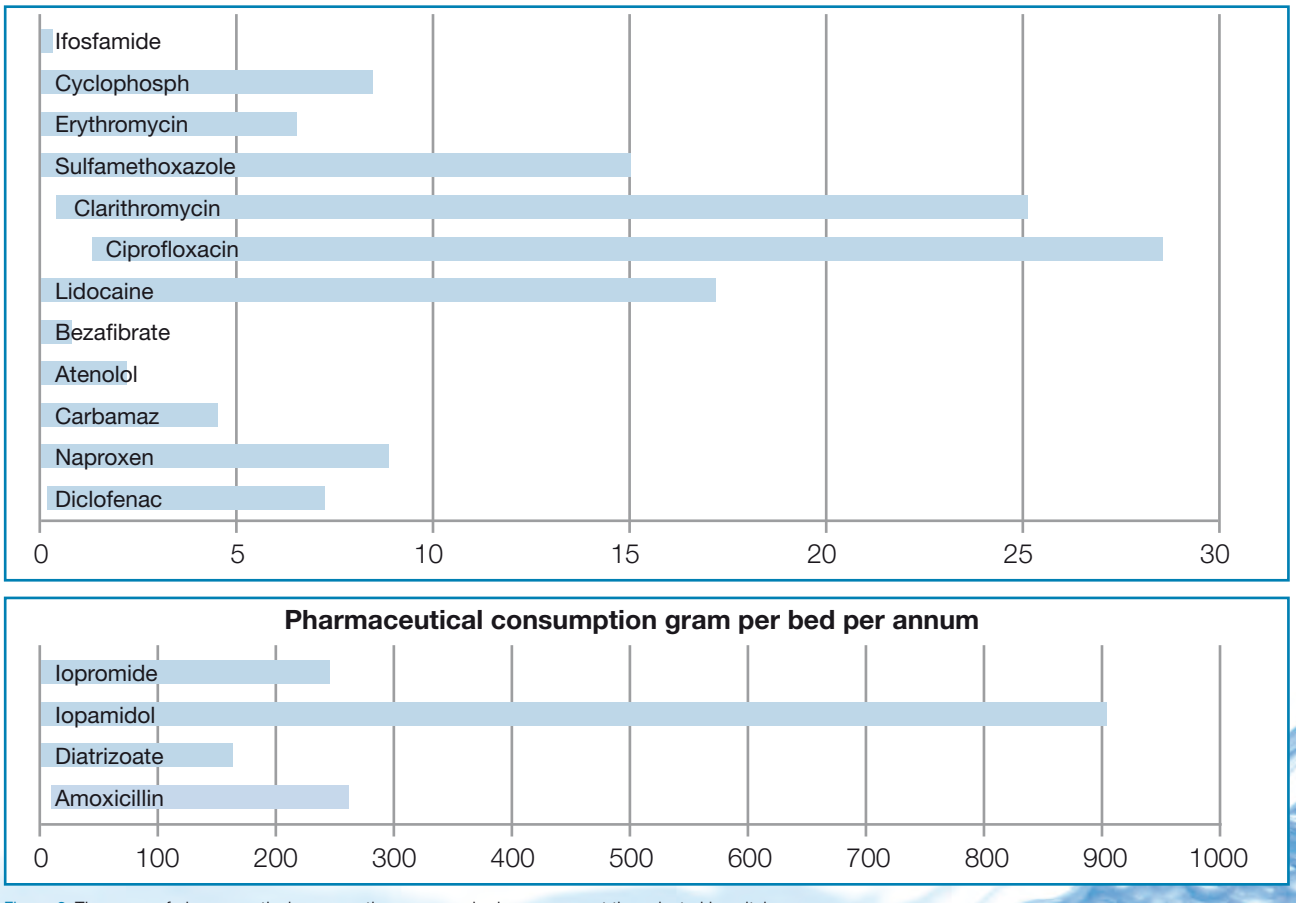


Figure 2: The range of pharmaceutical consumption gram per bed per annum at the selected hospitals

Figure 3 shows the range of the contribution of the investigated hospitals to the total pharmaceutical load flow in the catchment. Hospital contributions to the total load of pharmaceuticals in the respective investigated catchment areas (ratio of approx. 6.1 to 14.1 beds per 1,000 inhabitants) showed considerable variation - both between compounds and hospitals - but were highest for contrast media (40-100%), lidocaine (56-62%), and antibacterials ciprofloxacin (12-100%) and clarithromycin (12-60%). Hospital contributions for compounds for other treatment groups were below 20%.

relatively high number of elderly people in residential care will be using incontinence pads.

Ecotoxicological potential of hospital waste water

Table 1 gives an overview of the tests results regarding the toxicity potential of raw hospital waste water in comparison to municipal waste water. The tested raw municipal waste water was not cytotoxic or mutagenic. Raw hospital waste water samples showed average

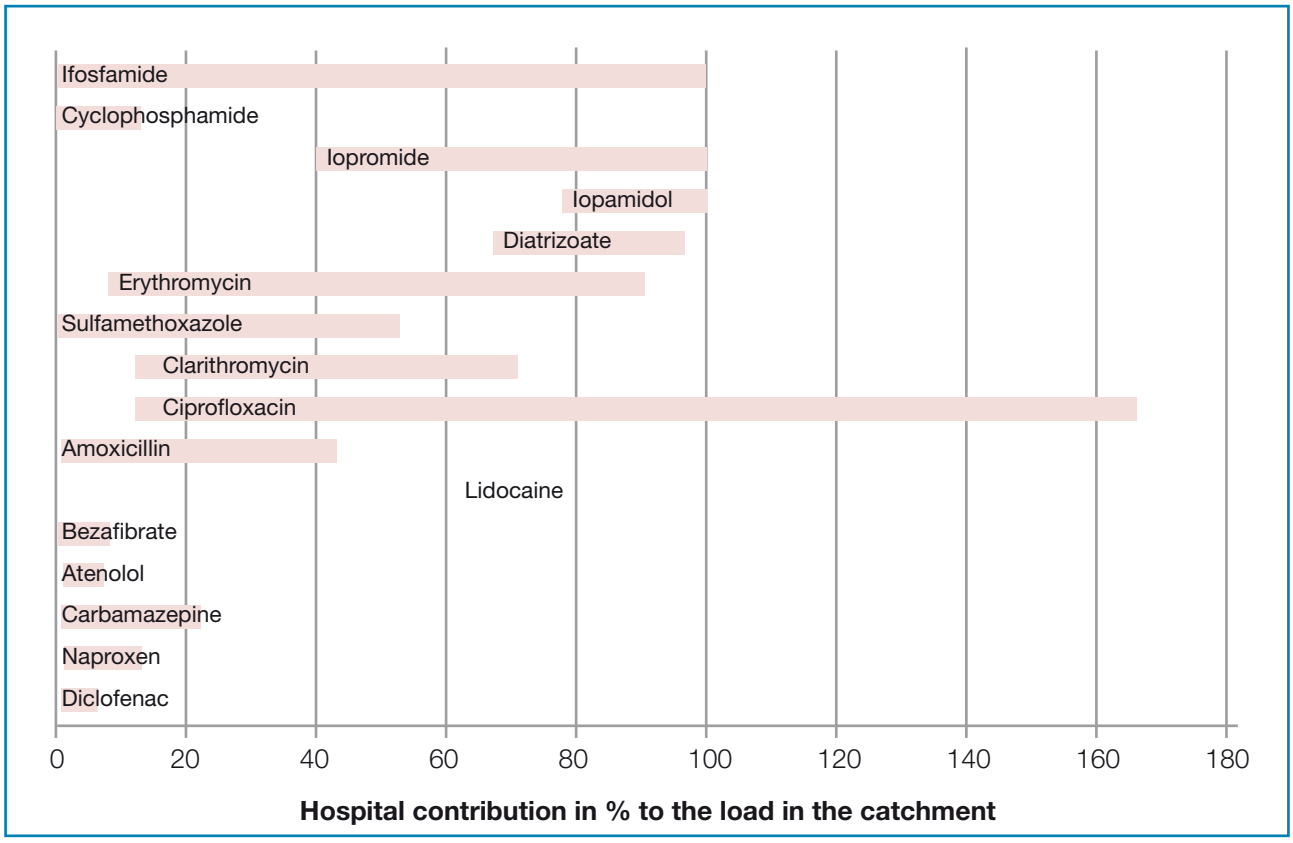


Figure 3: The range of hospital fraction of the selected compounds for three investigated hospitals as relative load of pharmaceuticals in the hospital compared to the load of the respective catchment area or in the connected municipal waste water treatment plant

Besides hospitals the relevance of other care facilities was evaluated by the Scottish partner. Their data suggested that pharmaceutical consumption in care homes for older people is lower than in geriatric hospitals, as, over a range of residential facilities open to elderly people, the geriatric hospital is likely to cater for those with the most serious health issues. With pharmaceutical consumption also generally lower than in general hospitals, the care home contribution is expected to be less important than the (general) hospital contribution. This expectation is further supported by considering that a

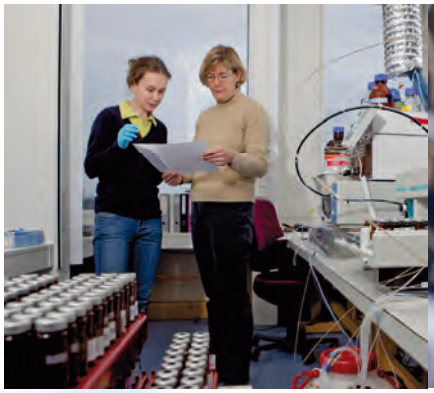
moderate cytotoxic and mutagenic effects. In all other tests raw municipal waste water, effluent of municipal waste water and raw hospital waste water from different locations had moderate or high toxic effects. Municipal waste water had a higher toxic effect on scuds than hospital waste water. In other tests hospital waste water was in comparison to municipal waste water more toxic to algae and to bacteria. Furthermore, hospital waste water had a higher estrogenicity than the tested municipal waste water.

Endpoints	Raw municipal wastewater	Effluent of municipal wasteland treatment plant	Raw hospital wastewater
Viability of cells			
Estrogen effects (EE2 equivalent)	19.7 ng/L		43 ng/L
Mutagenic effects			
Antibiotic effects			
Inhibition of luminescence (concentration Factor EC50)	0,72 - 1.26 fold	33.85 fold	0.26 - 0.84 fold
Inhibition of algae photosynthesis (concentration Factor EC50)	12.07 fold		1.97 fold
Inhibition of algae growth rate	34 %		64 - 88 %
Mortality of scuds	100 %		> 50 %

Samples of different locations tested different institutions. Evaluation ist performed on average values. Color codes:

	Cell viability in the cytotoxicity test (according DIN EN ISO 10993-5)	EC values based on expert judgment	other values (change of effect compared to negative control)
no negative effects	81 -100 %	EC50 > 100	< 5 %
weak or moderate effects	61 - 81 %	20 < EC50 < 100	5 - 20 %
Strong effects	0 - 60 %	EC50 < 20	> 20 %

Table 1: Toxicity potential of hospital waste water and municipal waste



Though, some in vitro bioassays can measure the effects of all substances in an environmental sample with the same mode of action, e.g. estrogenic substances. But, the detected toxicity effects cannot be related to individual chemical compounds. The toxicity tests therefore don't allow conclusions neither on the toxicity of specific single substances nor on the toxicity of the mixture of pharmaceuticals or other compounds. Some bioassay results showed a high variability which may be related to the highly variable nature of the composition of hospital waste water and the different source from other waste water treatment plants. The variable composition of hospital waste water and the dilution effects in municipal waste water may also be the reason for the higher toxicity of hospital waste water when compared to municipal waste water.

Antibiotic resistant bacteria in hospital waste water

Both, the quantity of antibiotic resistant integrons (representing the importance of antibiotic resistance in an environment independently of the quantity of bacteria) and the proportion of bacteria harbouring a resistant integron in the same sample (the relative abundance) were measured. Figure 4 shows the range of the measured concentrations of resistant integrons and the proportion of bacteria with resistant integrons in hospital waste water, in a domestic waste water and in two rivers. The variations in the measured values of hospital waste water were probably due to the different hospital practices, configurations, sizes, etc. A similar variability was observed for the relative abundance. As antibiotic resistant integrons are embedded on mobile genetic elements generally present in further copies, the relative abundance can be higher than 100%. Specialised medical centres with geriatric and psychiatric activities were not sources of bacteria harbouring resistant integrons.

The elevated concentrations and relative abundance of hospital effluents (5 to 390%) when compared to the investigated rivers (0.6 to 1.9%) showed that the hospitals are a potential source of multidrug resistant bacteria. Furthermore, with regards to the relative abundance found in municipal waste water (13%) hospital effluents can be seen as a hotspot for antibiotic resistant bacteria.

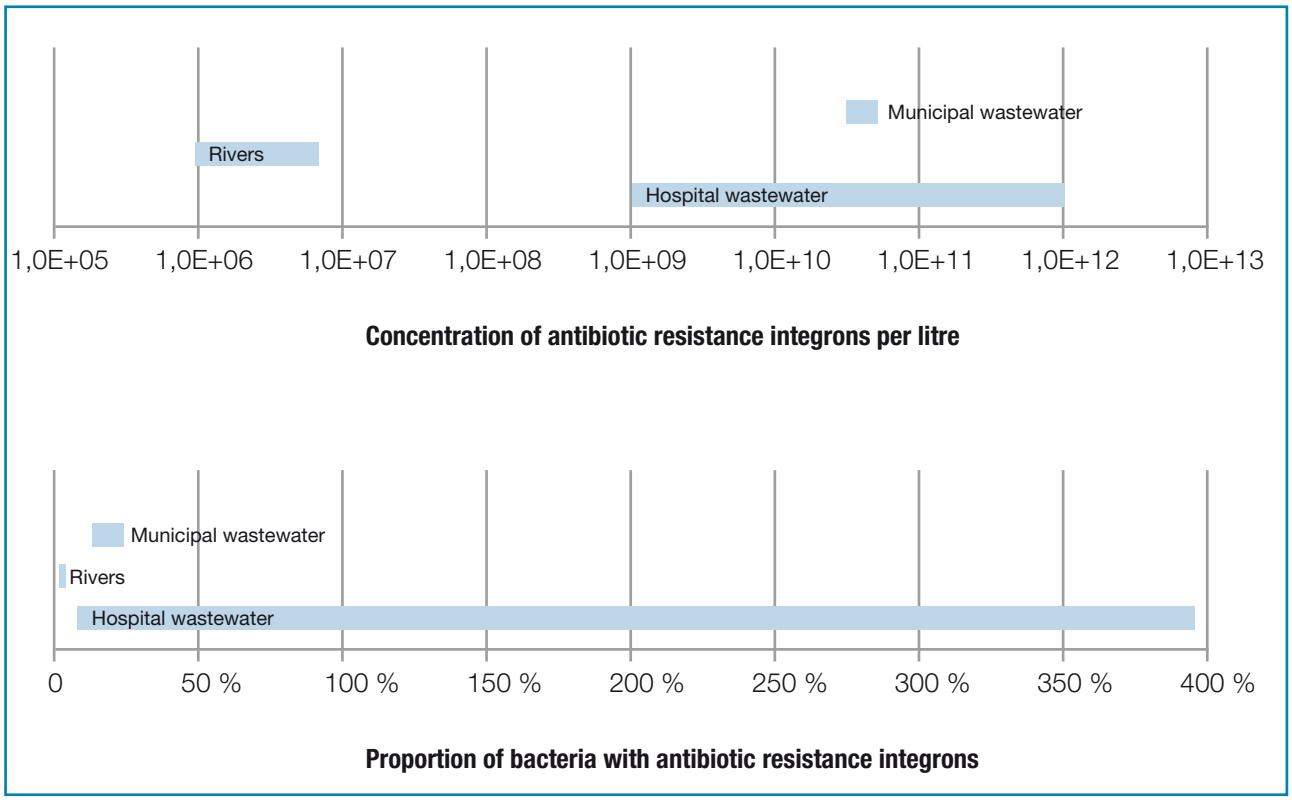


Figure 4: Concentration of antibiotic resistance integrons and proportion of bacteria with antibiotic resistance integrons in hospital waste water in comparison to municipal waste water and river water

German pilot facility

Germany: Marienhospital Gelsenkirchen

The German pilot plant receives waste water from the Marienhospital Gelsenkirchen, a typical hospital for a big German city with a wide range of services. This hospital has around 580 beds, about 1,150 employees and approx. 25,000 in-patients and 50,000 out-patients per year.

The pilot plant at Marienhospital Gelsenkirchen was designed for maximum inflow of 25 m³/hour and an average inflow of 200 m³/day. As the rainwater flow from the previously mixed discharge was disconnected, the full-scale treatment facility is provided mainly with concentrated hospital waste water. The waste water pilot plant consists of a biological waste water treatment in a membrane bioreactor (MBR) and subsequent full-scale waste water advanced treatment by ozonation and powdered activated carbon addition (with post-treatment by sand filtration). The pilot plant has the permission to discharge the treated water into an open water body close to the hospital.

The treatment facility is located in its own separate building behind the hospital, designed to stay in place and operate even after the completion of PILLS, offering the option to continue both with research activities and follow-up projects. The facility is operated by the Emschergenossenschaft.

The Netherlands: Isala Clinics

The Isala clinics in Zwolle are situated at two locations: Weezenlanden and Sophia. Currently, the location Sophia is extending in order to concentrate all departments at one location and Weezenlanden will ultimately be closed. Isala is the 5th largest non-academic hospital in the Netherlands. It employs 5,700 people, has 1,076 beds, 470,000 polyclinic visits and 40,000 hospitalisations per year. In recent years Isala developed more and more highly specialised functions.

Dutch pilot facility

With an hourly average design flow of 10 m³/h the pilot plant at Isala should treat in average 240 m³ per day. The facility is on a site in the neighborhood of the hospital and operates as a full-scale plant for the complete waste water flow. The pilot plant consists of a biological waste water treatment in a membrane bioreactor and a subsequent full-scale granulated activated carbon filtration. Post-treatment by ozone oxidation, UV/H_2O_2 oxidation unit and reverse osmosis filtration have been investigated at pilot scale. The permission for the treatment facility is asking for discharge of the treated waste water back into the sewer system. The partner in charge for the operation is the Waterschap Groot Salland.

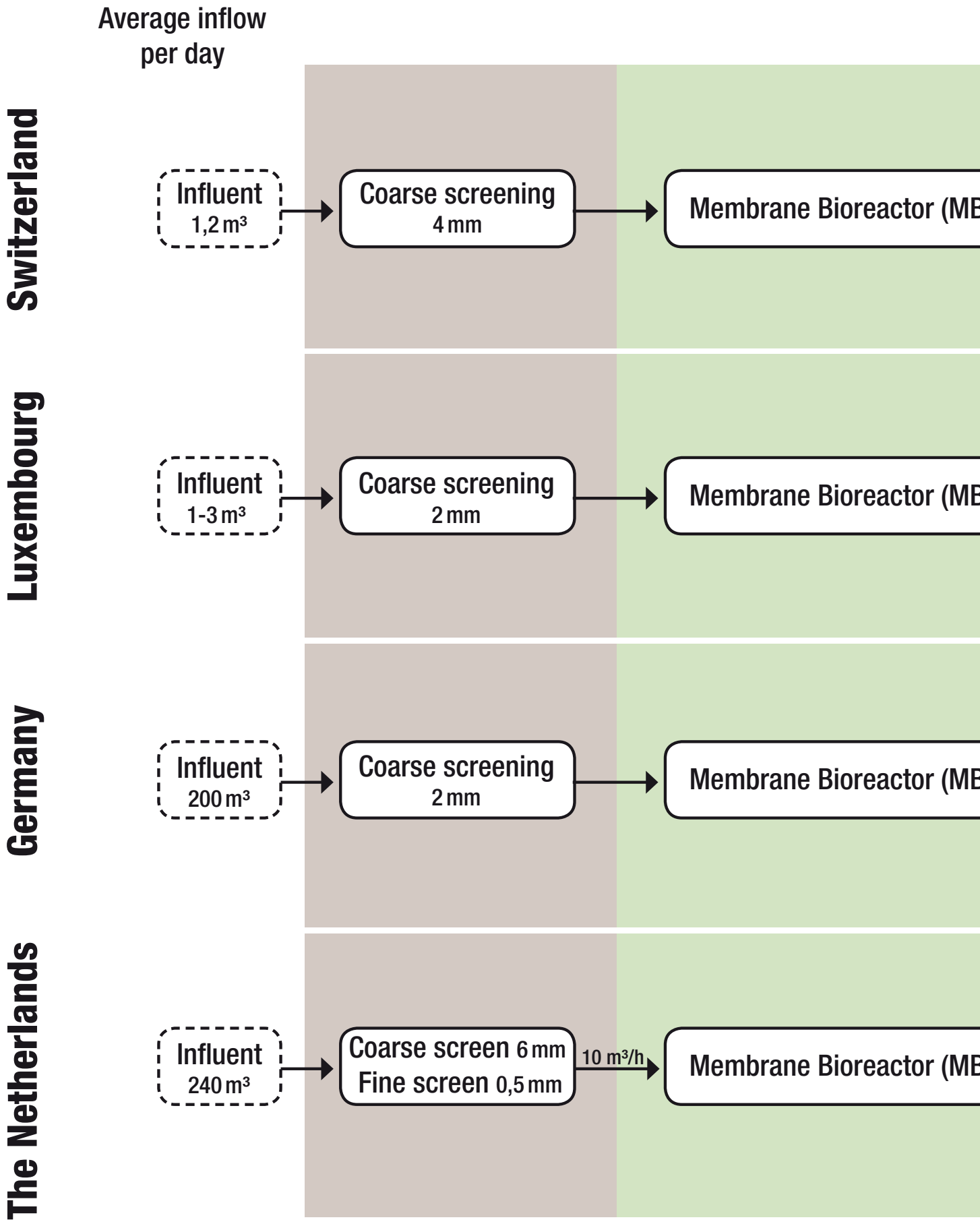
Switzerland: Cantonal Hospital of Baden

The cantonal hospital of Baden is a typical, regionally important general hospital in Switzerland with 346 beds serving more than 250,000 inhabitants in a decentralized area. In 2009, there were 126,328 “days of care”. The whole range of medical services is offered. Around two thirds of the X-rays that were carried out were performed on out-patients.

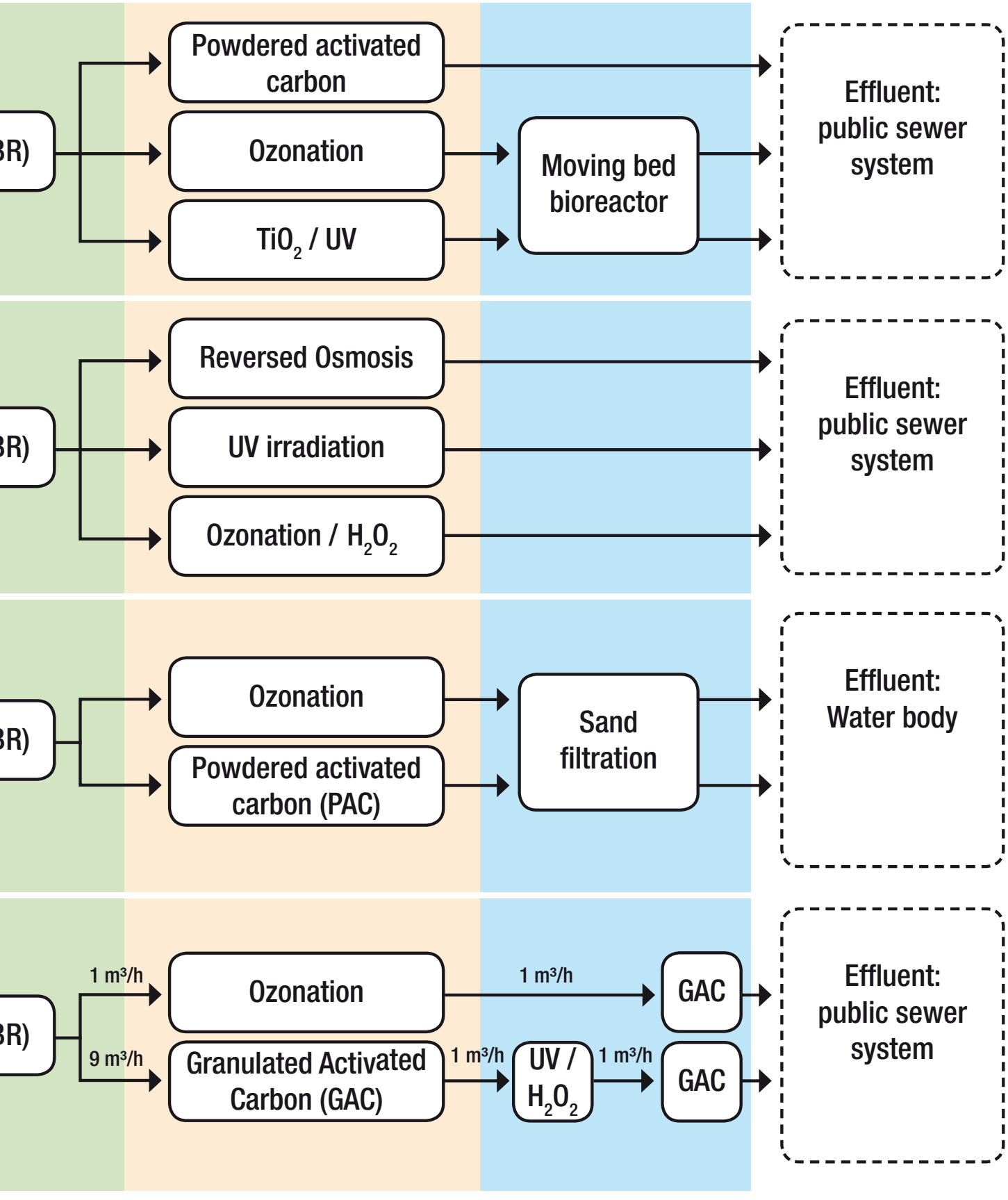
In 2009, 203,368 m³ of water was used in total, of which 84,987 m³ (233 m³ per day) in the main hospital wing that hosts patients, where pharmaceuticals are excreted. At this location, the waste water from the restaurant is included, but not that from the laundry facility.

The Swiss pilot plant constructed and investigated by Eawag, was completely funded via national funds but operated during the PILLS project and thus contributed to the joint work. It was located in basement rooms of the hospital, designed for temporary operation, treating partial flows of the hospital waste water.

Schematic illustrat



tion of the pilot plants



Swiss pilot facility

The main biological treatment comprises an MBR. Ozonation, oxidation with UV/TiO_2 and powdered activated carbon addition were investigated for the treatment of the MBR permeate. As a final step, a biological post treatment in a moving bed bioreactor was included to reduce oxidation by-products.

Luxemburg: Centre Hospitalier Emile Mayrisch (CHEM)

The Public Research Centre Henri Tudor built a pilot plant at the hospital Centre Hospitalier Emile Mayrisch (CHEM). In total the CHEM has 640 beds and 360 beds are located at the hospital that was investigated in Esch-sure-Alzette.

The pilot plant treated partial flows of the hospital waste water and was designed for only temporary operation hosted in a container close to the hospital. The main biological treatment consists of an MBR. Two advanced oxidation processes UV/H_2O_2, O_3/H_2O_2) and reverse osmosis were used to treat the MBR permeate.

All pilot plants are characterised by a combination of technologies, which has the objective of eliminating the largely persistent residues of medicinal products in addition to the biodegradable substances and nutrients. For this reason conventional waste water treatment processes are applied in the PILLS plants which are complemented by advanced techniques.

Characteristic of each design is that the core technology comprises membrane bioreactor (MBR) followed by advanced physical-chemical (UV, Ozone, Activated Carbon, advanced oxidation processes, reverse osmosis) treatment methods.

The performance of the pilot installations is evaluated in terms of removal efficiencies for pharmaceutical substances, the 'classical' parameters (COD, BOD, N, P) as well as the energy consumption. Further performance evaluation with regard to ecotoxicity and antibiotic resistance are described, too.

Luxemburg pilot facility

ADVANCED WASTE WATER TREATMENT – THE TECHNIQUES

Ozone
Ozone is an oxidant used widely for the disinfection of drinking water but can also be used for waste water polishing. The ozone dosages applied in post treatment of waste water will result in the formation of oxidation products. These products can be toxic or persistent to biodegradation.

Advanced Oxidation Processes
Advanced Oxidation Processes (AOPs) are combined processes aiming mainly at formation of the hydroxyl radical (OH•). The OH-radicals are strong non-selective oxidants. They can oxidize pharmaceuticals but also other organic compounds. Formation of oxidation products is expected and should be researched with respect to their toxicity and biodegradability. The AOPs investigated for advanced waste water treatment are UV/Ozone, UV/H_2O_2, Ozone/H_2O_2, Fenton reactions and UV/TiO_2. In general, it is expected that the addition of H_2O_2 to the ozonation unit will result in only a slightly higher removal of pharmaceuticals.

UV/Ozone and UV/H_2O_2
The UV-light is used for the disinfection of drinking water or waste water. To oxidise compounds UV is used in combination with ozone or H_2O_2 to produce OH-radicals. These AOPs are comparable to the ozone/ H_2O_2 process. Therefore the costs of both processes might be most important for the optimal choice.

Fenton reactions ((UV)/ H_2O_2/Fe^{2+} or Fe^{3+})
The use of a catalyst (iron) in appropriate environmental conditions can intensify the hydroxyl radical yield.

UV/TiO_2
The TiO_2 photocatalyst is activated by UV light. The use at ambient temperature and pressure represents a particular advantage of this AOP process. One of the challenges of this method is the separation of the particulate catalyst from the treated waste water.

Activated carbon
In the treatment with activated carbon, the contaminants are sorbing to the surface of the carbon. Either powdered activated carbon (PAC), or activated carbon filtration (the filter consisting of granular activated carbon, GAC) is used. This technology is well known for the purification of drinking water.

Reverse osmosis
In reversed osmosis (RO) the pharmaceuticals are hold back by a dense membrane. The permeate of the MBR was used as feed for the reverse osmosis membrane installation.

Oxidation with ferrate
Ferrate (Fe(VI)) can be used to oxidize micropollutants. Experiments were performed with model waste water and real waste water.

All initiatives of the partners aimed at practical outcomes to achieve optimized treatment results while maintaining a good cost-benefit. It was clear from the start of the project that contributions to European environment policy should not only consider waste water treatment outcomes but potential impacts on other media, too, such as energy consumption, waste and transformation products, operation and simply suitability.

Different assessment methods evaluating the individual advanced treatment techniques of the pilot plants are:

Performance in reducing pharmaceutical concentrations

The respective plant configurations and advanced treatment processes are compared with regards to their purification efficiency. This research will show which method is best suited in the respective situation to eliminate specific pharmaceuticals. Furthermore, their efficiency regarding the reduction of ecotoxicological effects and of antibiotic resistant bacteria is investigated.

The MBR pretreatment leads to a good wastewater quality in terms of COD, nutrients and bacteria removal and is an important first

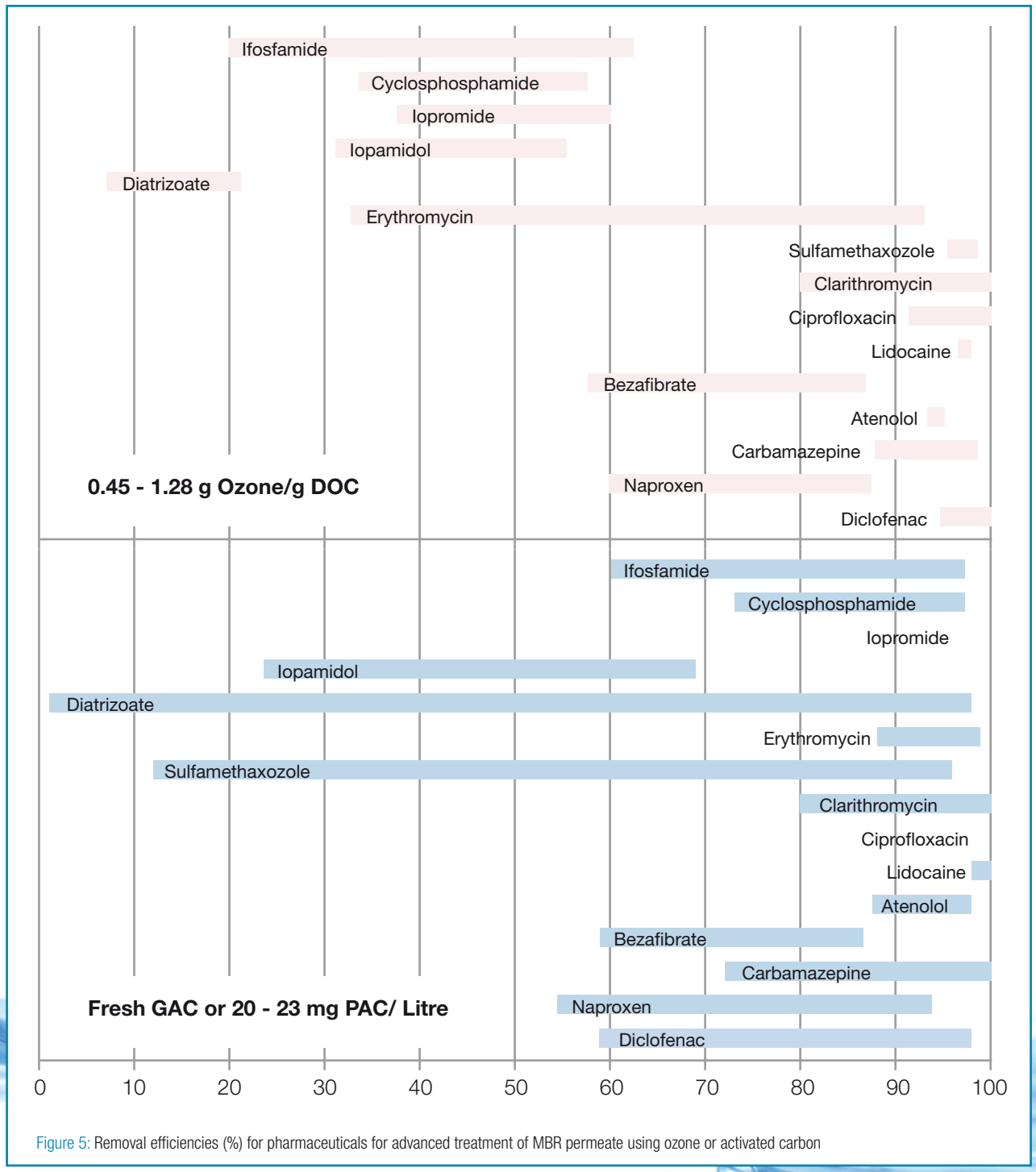


Figure 5: Removal efficiencies (%) for pharmaceuticals for advanced treatment of MBR permeate using ozone or activated carbon

step of decentralized advanced wastewater treatment. Half of the analyzed compounds were removed to less than 50% by the MBR. An elimination of 80% could be achieved for most compounds with the treatment with 0.5 g O_3/g DOC (except for cyclosphosphamide, ifosfamide and the X-ray contrast media diatrizoate, iopamidol and iopromide) and 20 mg/L PAC (except for sulfamethoxazole and the X-ray contrast media diatrizoate and iopamidol).

Activated carbon filtration led to elimination rates of >95% for all compounds with a fresh GAC filter (Figure 5). High elimination could also be achieved with RO. UV/H_2O_2 applying a fluence of more than 47,250 J/m² effective to remove >77% of all the analyzed pharmaceuticals. For the biological treatment energy consumption of the pre-treatment step of 0.3-0.6 kwh/m³ and the MBR step of 0.9 kwh/m³ are predicted. Energy consumption of PAC (0.45 including sand filtration) was higher than for GAC (0.2 kwh/m³). Energy consumption for UV treatment was between 0.5 and 1.0 kWh/m³, which is higher than for the treatment with ozone (ranging from <0.2 to 0.9 kWh/m³). Energy consumption for RO was more than 1.0 kWh/m³.

Performance in reducing ecotoxicological effects

Ecotoxicological assessments were carried out with the different effluents produced. The test battery used consists of various short-term and long-term toxicity tests considering different aquatic trophic levels and representing functions. It includes in-vitro screening tests for the assessment of specific effects (e.g. cytotoxicity or endocrine disrupting effects) and general toxicity to bacteria and algae

Bioassays	Endpoints	Effluent of MBR	MBR + O3	MBR +O3 + SF	MBR +PAC/SF
A-YES test (AQUA 1.0)	Estrogenicity (EE2 equivalent)	0.235 ng/L	0.261 ng/L	0.176 ng/L	0.079 ng/L
Ames test (Salmonella thyphimurium, strain YG7108)	Mutagenicity (No. of histidine revertants)		↑	↘	
Bacteria test (Vibrio fischeri)	Inhibition of luminescence (concentration factor EC50)	↓	↓	↘	↓
Algae growth test (72hr)	growth rate inhibition, average for dilutions 80% and 50% wastewater	↓	↗		

Bioassays	Endpoints	Effluent of MBR	MBR + O3	MBR +O3 + GAC	MBR +GAC	MBR + VU	MBR +VU +GAC
Waterscan (antibiotics test)	Sulfanomides (concentration factor EC50)						
Bacteria test (Vibrio fischeri)	Inhibition of luminescence (concentration factor EC50)			↓	↓		↓
Algal photosynthesis test (4.5 and 24hr)	Inhibition of photosynthetic efficiency (concentration factor EC50)					↓	↓

Evaluation is performed on average values. Change of toxicity value after treatment process: ↑ and ↓ indicate increasing toxicity or decreasing toxicity of > 20%, ↗ and ↘ indicate slightly increasing toxicity or slightly decreasing toxicity of < 20%. Color codes:

	EC50 values based on expert judgment	Other values (change of effect compared to negative control)
no negative effects	EC50 > 100	< 5%
weak or moderate effects	20 < EC50 < 100	5 - 20%
Strong effects	EC50 < 20	> 20%

Table 2: Evaluation of the performance of treatment processes measured in bioassays (extract).

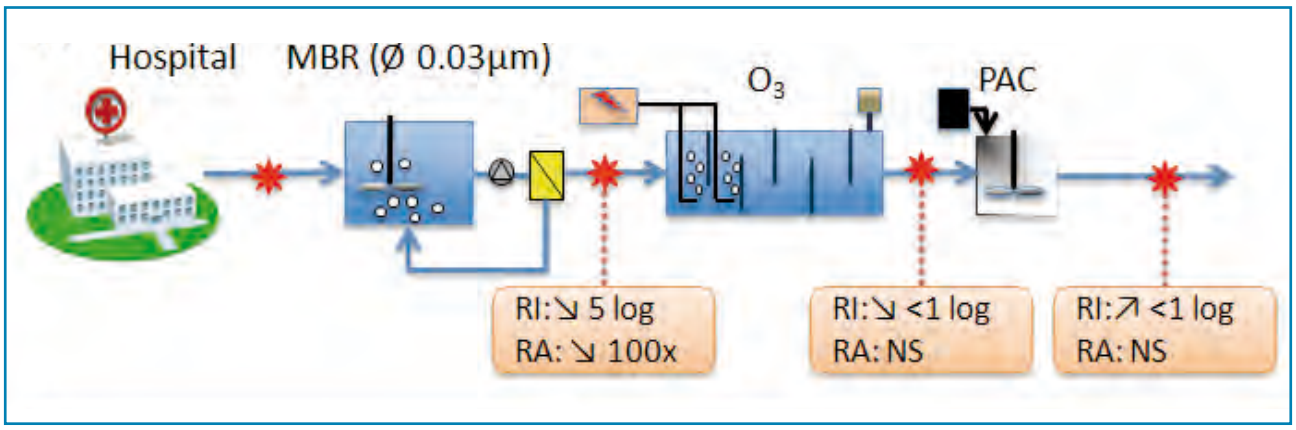
as well as in-vivo tests on organisms like snails, worms, water fleas or fish. With these tests the effects of all substances in the water, as well as their interactions, are taken into account. Also possible effects of generated by-products may be measured in this way.

Some results of the bioassays performed by different institutions with the samples of the different pilot plants are shown in Table 2. The biological treatment in the MBR decreased the toxic effects in raw hospital wastewater. But, MBR permeate was still toxic to some organisms like bacteria, algae and snails. The advanced waste water treatment by activated carbon had in general decreasing effects on the toxicity of raw waste water, but the effluent of this treatment process may still contain algal toxic compounds. Ozonation reduced antibiotic and estrogenic effects of hospital waste water. However, in some bioassays increasing toxicity was measured the oxidation processes by ozonation or UV treatment, presumably due to the formation of by-products. A post-treatment of the ozonationVbiofilter could reduce the adverse effects of the oxidation significantly but did not remove it totally. Also the subsequent sand filter was not as efficient as observed at previously evaluated treatment plants to reduce oxidation product induced toxicity. GAC filtration was found efficient to remove the adverse effects of the UV treatment effluent.

Performance in reducing antibiotic resistant bacteria

By measuring the amount of antibiotic resistant integrons, the presence of multi resistant bacteria in hospital waste water was proved. A distinction can be made for the extent to which bacteria are resistant, i.e. how many antibiotics they are resistant to. Also the proportion of bacteria containing antiobiotic resistant integrons was determined.

The efficiency of advanced wastewater treatment processes to remove antibiotic resistant integrons was between 1 to 5 log, mostly due to the elimination efficiency in the MBR with membranes pore sizes of 0.03-0.04 µm. The effect of advanced treatment with ozone or activated carbon on the reduction of the resistant integrons and their relative abundance in waste water was negligible compared to the efficiency of MBR with ultrafiltration membrane.



Decreasing (↘) or increasing (↗) rates of the initial concentration (in log10 factor) of resistant integron (RI), and its associated relative abundance (RA) given in fold factor (x). NS: not significant.

Figure 6: Evaluation of the performance of treatment processes for the reduction of antibiotic resistant integrons and their relative abundance in the waste water (extract)

Cost assessment

In addition to the efficiency, the costs incurred from the construction and operation of the plants is of particular significance. For this reason the plants are subjected to a cost assessment in which both the overall costs and the costs of the different further treatment processes are compared. The annual investment costs and operational costs are determined for this purpose.

As the investigations in the PILLS project were carried out with installations especially designed for this purpose, in some case extra

	MBR	MBR + GAC	MBR+O3+GAC	MBR+UV/H2O2+GAC
Investment cost	3.25	3.35	3.50	3.65
Variable cost	1.45	1.65	1.75	1.85
Total cost	4.70	5.00	5.30	5.50

Table 3: Costs in Euro/m³ for treatment of hospital wastewater with different treatment techniques calculated for the NL situation

equipment was installed, solely for the purpose of the researches. If a new treatment facility were to be designed, exclusively for the treatment of hospital wastewater, it would be different. The cost figures presented in Table 3 indicate the cost level for construction and operation of a new on site treatment installation of hospital wastewater. The costs of GAC and PAC are comparable.

Life-cycle assessment

A life-cycle assessment methodology normally considers the three steps of the life-cycle: the construction, the operation phase and the dismantling. In this particular case, because this life-cycle assessment aims at comparing scenarios having similar infrastructures, the first and the last phases of the life-cycle can be neglected. Only the indirect pollutant emissions due to the operation of the plant, i.e. those generated by energy and raw materials consumption and production, are considered. The environmental impact is calculated by the Luxemburgish partner for many impact categories (global warming potential, acute and chronic ecotoxicity in water, carcinogenic effects and others) to broaden the possibility of comparison.

From LCA point of view there was no significant difference between centralized (with or without advanced treatment) and additional decentralized advanced treatment for the elimination of pharmaceuticals because in LCA the toxicity impact of pharmaceuticals has been observed to be negligible compared to other impacts, like nutrient removal (with the effect of avoided eutrification). However, considering the overall environmental impacts in a LCA ozonation (by low energy consumption) was found more efficient than activated carbon treatment; and activated carbon more efficient than ozonation (by high energy consumption) and UV treatment.

Multi-criteria (decision) analysis

The partnership had originally planned to carry out a multi-criteria decision analysis. Finally, after nearly 5 years of discussions and considering different approaches, even with experts support, the partners decided that a Multi-Criteria Decision Analysis (MCDA) achieving serious scientific results is not possible under the given circumstances. There are a number of reasons for this: in particular the differing political, cultural and administrative decision levels in the countries: Who decides what? How to weigh indicators? What is the decision about?

The MCDA approach was scientifically designed to support a clear decision on a best solution in a specific case – this is not achievable given the PILLS problematic. There seem to be always several options to take and a “best solution” cannot be recommended at present.

However, the PILLS partnership is convinced that they feed into the discussion process on a European level and the work to data gives clear hints and arguments about what is helpful under which conditions. In this sense PILLS offers a multitude of “decision support” – solutions and choices are now depending on the criteria that are prioritized under local conditions by the stakeholders.

CONCLUSIONS

Concentrating on the essential title of the project - Pharmaceutical Input and Elimination from Local Sources - the following arguments are cognitions by all partners::

POINT SOURCE

- Hospitals are a “hot-spot” because here there is a high load of pharmaceuticals used and emitted through hospital waste water into the municipal sewerage.
- However, the fraction of pharmaceuticals distributed in hospitals compared to what is distributed in the communities is relatively low (around 20%).
- Certain pharmaceuticals (X-ray contrast media, cytostatics and some antibiotics) are distributed in much higher amounts in hospitals than at home. This offers the opportunity to eliminate high amounts of these specific pharmaceuticals from the environment by decentralised hospital waste water treatment plants.
- The contribution of the hospital is different for each waste water treatment plant catchment, depending on the amount of beds and natural inhabitants connected to the facility. The range normally found varies between 5-50 beds per 1000 inhabitants.
- Geriatric hospitals do not emit the expected high load: measurements and interviews for this specific case are showing that no comparable situation to hospitals discharge levels occurs because of the use of liners/diapers/pampers.

TECHNOLOGY

- Advanced treatment is necessary to eliminate most pharmaceuticals from waste water. Biological treatment is not enough.
- Treatment with biological treatment (e.g. a membrane bioreactor) plus ozone and/or activated carbon or UV/H_2O_2 or reverse osmosis was found to be effective to achieve this elimination.
- The MBR pretreatment leads to a good wastewater quality in terms of COD, nutrients and bacteria removal and is an important first step of decentralized advanced wastewater treatment. Half of the analyzed compounds were removed to less than 50% by the MBR.
- With the advanced treatment with ozone or PAC an elimination of 80% could be achieved for most of the investigated compounds, but not for all of them. Activated carbon filtration with a fresh GAC filter and RO led to high elimination rates for all compounds. The advanced oxidation process UV/H2O2 was effective to remove all the analyzed pharmaceuticals by used of a high fluence.
- Energy consumption for UV treatment was higher than for the treatment with ozone. Energy consumption for RO was more than 1.0 kWh/m³.
- Total costs of decentralized hospital waste water treatment of 4.70 €/m² (for MBR) to 5.5 €/m³ (MBR+UV/H_2O_2+GAC) and variable costs between 1.45 €/m³ (MBR) and 1.85 €/m³ (MBR+UV/H_2O_2+GAC) were calculated.
- MBR decreased toxic effects in raw hospital wastewater, but the effluent still may contain toxic compounds to some organisms. Decreasing effects are observed by the advanced waste water in the most bioassays. But, in some bioassays increasing toxicity is measured after oxidation processes, presumably due to transformation products. These negative effects could be reduced by a subsequent biofilter or GAC filter, but not totally in the subsequent sand filter.
- MBR treatment leads to a significant reduction of antibiotic resistant integrons. Additional advanced waste water treatment by ozonation or activated carbon after the MBR with ultrafiltration membranes had no significant influence on the reduction of the resistant integrons.
- From life cycle analysis (LCA) point of view the toxicity impact of pharmaceuticals has been observed to be negligible compared to other impacts, like nutrient removal (with the effect of avoided eutrification).
- The Comparison of the advanced treatment technologies (from best to worst) considering the overall environmental impacts in a LCA results in the following order: ozone (by low energy consumption) > activated carbon > ozone (by high energy consumption) > UV

RISK POTENTIAL

- The ecotoxicological risk of municipal waste water was found lower than of hospital waste water.
- The diversity of gene cassettes is lower in hospital waste water than in municipal waste water, but the proportion of multi-resistant bacteria (measured by integrons) in the bacterial community is higher in hospital waste water than in municipal waste water.

- A risk potential is caused by pathogens and antibiotic resistant bacteria in hospital waste water.
- Sewer overflows from municipal sewer systems may lead to discharge of hospital waste water into the receiving waters; a potential risk of spreading the mentioned resistant bacteria and pathogens.
- Treating at the source reduces risks for groundwater and surface water bodies.

MULTI CRITERIA DECISION ANALYSIS (MCDA)

A scientifically sound MCDA could not be developed within PILLS. The following criteria however may contribute to support decisions for decentralized hospital waste water treatment:

- Treatment efficiency,
- Energy consumption
- LCA
- Costs
- Antibiotic resistant bacteria / ecotoxicity
- Operation experiences and responsibilities
- Legal compliance
- Local aspects


FURTHER ACTIONS FOR A SUSTAINABLE REDUCTION

It is apparent that there is still a lot more research needed for a comprehensive assessment within this field. However, many involved participants agree that for precautionary reasons, action is necessary now. They also agree on the fact that that substances with a potential ecotoxicological risk are to be avoided as far as possible, or reduced to the extent that they have no effect. In this context, the benefits (quality of life) and damage (risk to humans and the environment) need to be taken into account.

It is, however, undisputed, that waste water treatment is not able to reduce the burden to the environment sustainably. Once these micropollutants have reached the waste water, their complete elimination is hardly reasonable – even if, in many cases, a low enough concentration is achieved so that their appearance is below the detection limit, or they have no (measurable) effects. This is the reason why an integrative strategy is necessary, that takes into account the entire life-cycle of the substances examined, from the production, to the points of use, to the disposal.

Possible measures to minimise pharmaceutical residues at the source:

- Legislative body: The creation of incentives which promote the use of more environmentally friendly substances in the manufacture of medicinal products. Furthermore, establishing a framework for the emissions of pharmaceutical substances to the environment would be a good first action.

- Pharmaceutical industry: Taking into consideration the possible environmental effects of individual active substances already in their development and performing targeted research in this field.
- Health professionals: Further training for health professionals concerning the long-term change of prescription practice so that overall, fewer or – where possible – "more environmentally friendly" medication is used.

- Medical centres, hospitals and nursing homes – so-called point sources: Waste water separation and local treatment of the waste water where high concentrations of pharmaceutical residues are encountered.

- Waste water management companies and drinking water providers: Advanced waste water treatment and improved drinking water purification helps to eliminate residues.

Lead Partner
Emschergenossenschaft
Kirsten Adamczak
Kronprinzenstraße 24
45128 Essen, Germany
Phone: 0049 - 201 104 2606 / 2679
E-mail: adamczak.kirsten@eglv.de

Germany
Emschergenossenschaft
Dr. Issa Nafo
Kronprinzenstraße 24
45128 Essen
Phone: 0049 - 201 104 2779
E-mail: nafo.issa@eglv.de

The Netherlands
Waterschap Groot Salland
Dr. ir. Herman Evenblij
Dr. Van Thienenweg 1
8025 AL Zwolle
Phone: 0031 - 38 455 7431
E-mail: hevenblij@wgs.nl

Luxembourg
CRP Henri Tudor
Dr. Alex Cornelissen
Schlassgoart 66, rue de Luxembourg
4002 Esch-sur-Alzette
Phone: 00352 - 545580 519
E-mail: alex.cornelissen@tudor.lu

Switzerland
Eawag
Dr. Christa McArdell
Ueberlandstraße 133
8600 Duebendorf
Phone: 0041 - 44 823 54 83
E-mail: christa.mcardell@eawag.ch

United Kingdom / Scotland
Glasgow Caledonian University
Dr. Ole Pahl
Cowcaddens Road
Glasgow G4 0BA
Phone: 0044 - 141 331 3572
E-mail: O.Pahl@gcal.ac.uk

France
Université de Limoges
Prof. Dr. Christophe Dagot
33, rue François Mitterand
87032 Limoges
Phone: 0033 - 555 423 697
E-mail: dagot@ensil.unilim.fr

Scientific Board

- Mark Heggie (Scottish Environment Protection Agency, United Kingdom)
- Dr. Florian Keil (vorm.: Institute for Social-Ecological Research ISOE GmbH, Germany)
- Dr. Thomas Schwartz (Karlsruhe Institute of Technology, Germany)
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