# The story of

MEDicines Unwanted in WAter
MEDicijnen Uit het WAter
MEDizin Unerwünscht im WAsser

# MEDUWA-Vecht(e)

INTERREG-VA Projectnr. 142118

Sewer in Enschede, SHA, 2014

Banded demoiselle at the Vecht(e), SHA, 2014

Water recreation at the Vecht(e), SHA 2020

SHA, 2003

How a seemingly unsolvable issue can inspire innovation

INTERREG Deutschland Nederland
Europäische Union
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MEDUWA

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provinsje fryslân
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With thanks to the 27 project partners whose vision and commitment made MEDUWA-Vecht(e) a success.

The texts are based on information provided by the project partners.

Editors: Margarita Amador and Alfons Uijtewaal, Stichting Huize Aarde; Raissa Ulbrich, Osnabrück University; Caroline van Bers, The Integrated Assessment Society (TIAS) and Osnabrück University

Place and Date: Enschede/Osnabrück, Oktober 10 2020

To Tiago, Karlo, Felien and all other babies born during and after the project.

"I don't know why it is so difficult for some people who just don't see things in a new way when the time changes and concepts change. They don't change with it, they resist the change and they dislike it intensely. I've always thought that a good rational change is fun".

Eugene Parker
(Astrophysicist, developer of the theory of the solar wind)

# Everything that comes out of us returns to us sooner or later

The number of medicines excreted by humans and animals that end up in the environment is almost impossible to estimate. It is also unknown how much of this contamination returns to humans and livestock via water, food and air (from agricultural dust). What is certain is that this medicinal environmental cycle will increase in the coming decades through increased use of medicines and as a result of climate change.

It is also known that under the influence of processes in the body and the environment, every medicine is converted into dozens of new forms. Some medicines and/or their transformation products remain in the environment for years. They can spread over large distances and surfaces and accumulate in (ground) water, soil, sediment, (food) plants and animals. Furthermore, we see that due to the worldwide increase in the use of antibiotics and other antimicrobial agents, more bacteria, fungi, viruses, etc. are becoming resistant to several types of medicines. Resistant bacteria from sewage and manure pass on their resistance to other bacteria in surface water, drinking water and the soil.

There are indications that this chemical and biological contamination affects plants and animals in water and soil in several ways. These life forms are all important because they need each other to keep an area ecologically healthy. Negative consequences of this medicinal environmental cycle for public health are possible, but difficult to demonstrate.

Establishing environmental standards for these contaminants is difficult because their therapeutic benefits are paramount and little is known about chronic effects at low environmental concentrations. The environmental fate of transformation products is also poorly understood. Medicines and other chemicals can interact with each other (cocktail effect). It was discovered not long ago that antimicrobial medicines also in the environment promote the emergence of new forms of microbial resistance even at low concentrations. This contributes to the fact that infectious diseases can no longer be treated with the medicines currently available.

## Disclaimer

Based on the study of medicines and bacteria within the MEDUWA-Vecht(e) project, it is not yet possible to draw conclusions about risks to public health. No epidemiological studies have been carried out. Only 15 of several hundred medicines entering the environment have been analysed in the project, and of the many types of resistant bacteria, only one has been studied. Whether carriers of these types of resistant bacteria experience complications during treatment of an infection has not been studied. No research has been done into transformation products of medicines and into mixture toxicity. Nor has it been investigated whether the low concentrations of antibiotics in the pilot area of the German-Dutch Vecht(e) River contribute to the emergence of new resistant strains of bacteria.

# A problem is no longer a problem as long as there are visionaries

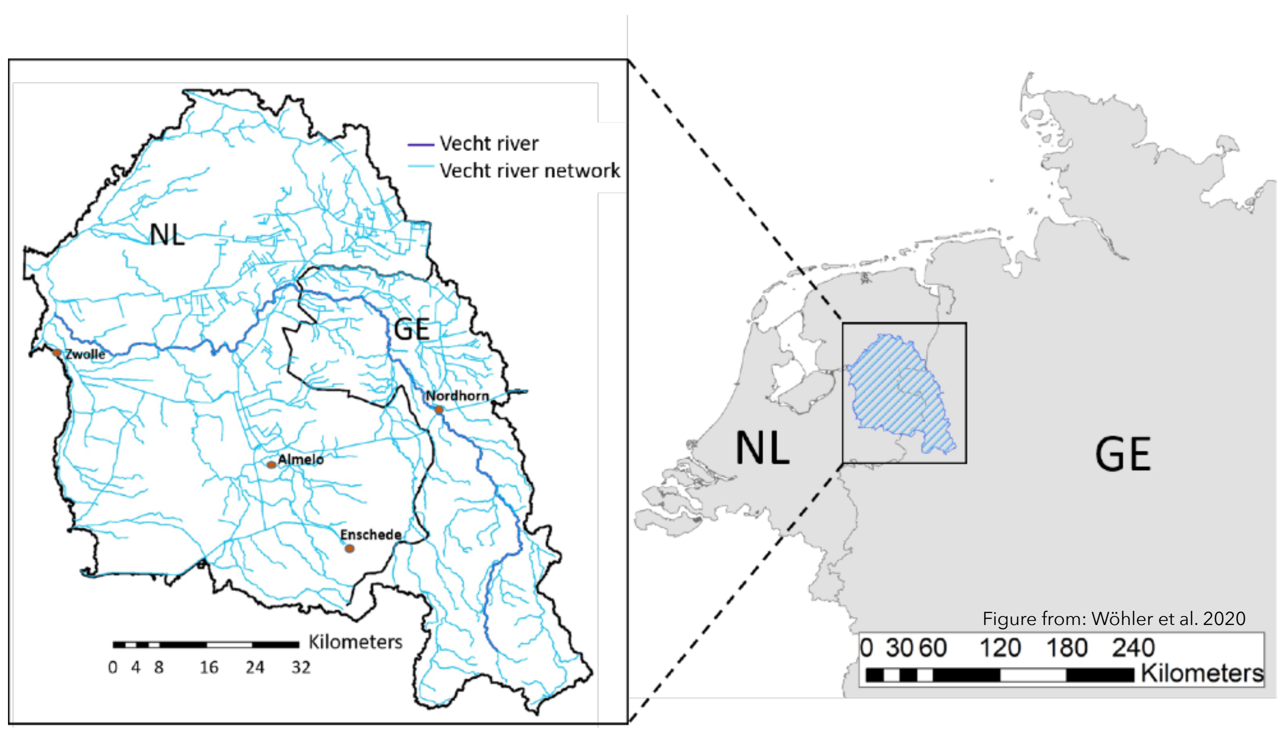
How do we solve the problem of the medicinal environmental cycle? Is it a problem of global proportions, which is invisible and has no obvious cause or solution? Is it a problem where, according to some, the knowledge of possible risks is insufficient to take action?

It is difficult to answer these questions satisfactorily because it is a relatively new field of research and there are still many knowledge gaps. According to the UN Agenda for Sustainable Development in the 21st Century (1992), broad-based research and development projects are needed to provide answers to such global challenges. In this century, there is an urgent need for new forms of communication and cooperation between scientists, visionaries and policy-makers.

The MEDUWA-Vecht(e) project consisted of a coalition of 27 project partners: 16 businesses, 8 research institutes, including two university hospitals, a water authority and two non-governmental organisations.

The 6,000 km2 catchment area of the German-Dutch Vecht(e), with hundreds of kilometres of river and 1.5 million inhabitants, was the pilot area for MEDUWA-Vecht(e).

The MEDUWA-Vecht(e) project ran from October 2016 to April 2021. The total costs were € 8.45 million, funded by the European INTERREG-VA programme: the European Union contributed €4.22 million, the regional authorities €1.79 million, and €2.44 million was contributed by the project partners themselves.

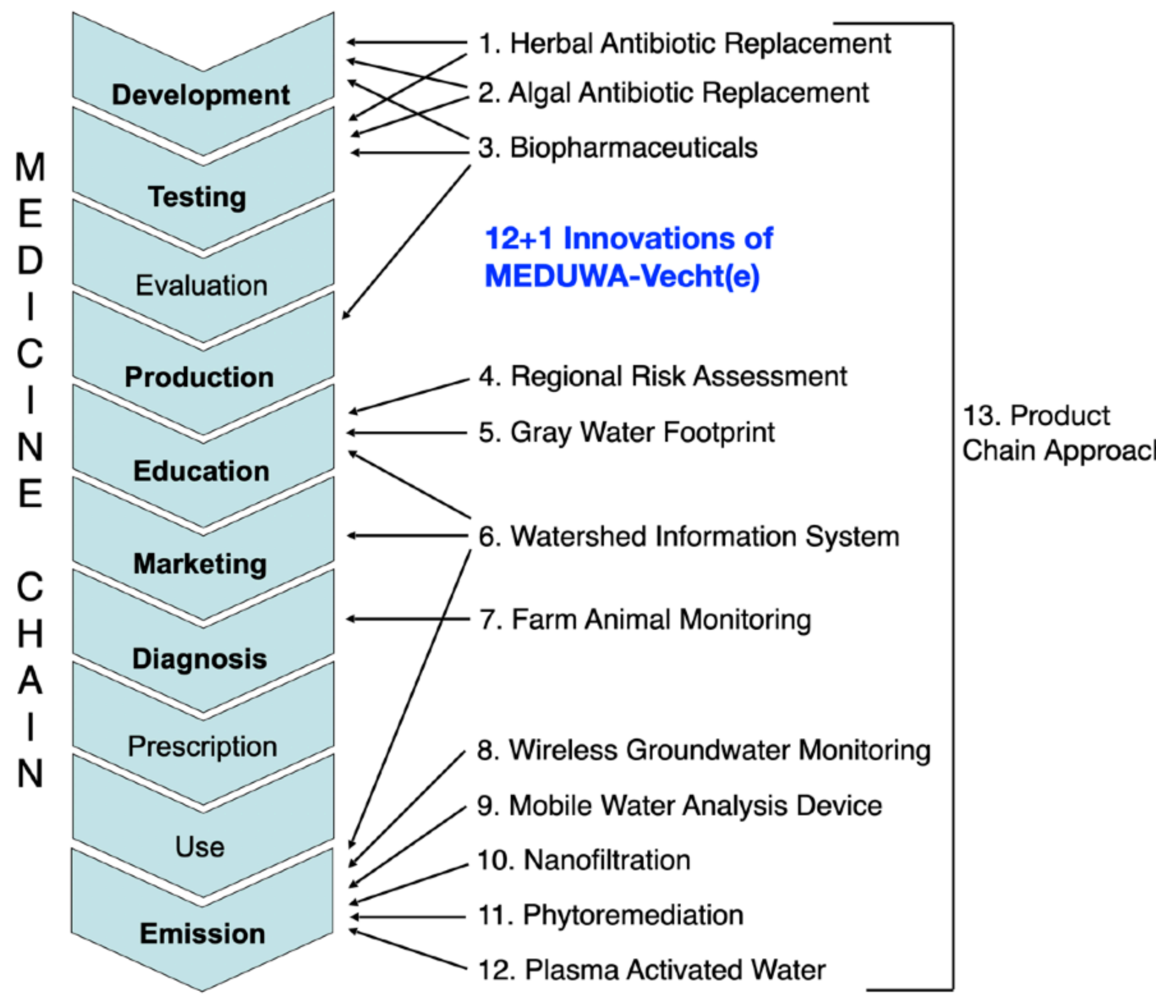



The cross-border watershed of the Vecht(e) river.

# No one can whistle a symphony alone

After more than four years of ongoing effort, it can be concluded that the MEDUWA coalition has produced new concepts, tools and models for the prevention, mitigation, measurement, monitoring, simulation, visualisation and communication of (solutions for) medicines and multi-resistant microorganisms in the environment. In total there were 12 innovations within 7 different links of the medicine chain.

Companies worked with research institutions in order to base their innovations on scientific evidence and to optimise performance. Tools were developed to assess and visualise the risks and evaluate the immediate effects of possible measures. Other tools can purify water and soil; stop pollution at its source; or continuously monitor animal health. Medicines that are biodegradable have also been developed for humans and animals. MEDUWA's 13th innovation, cooperation between multi-sectoral and multi-disciplinary partners in several levels of the medicine chain in a single project, has proven itself in practice.




Along the whole product chain, each of the researchers and entrepreneurs involved plays a central role in developing a package of mutually-complementary measures to reduce the problem of medicines in the environment.

# From global planning to local action

For an innovator, it is usually difficult to see which international, national or regional policies an innovation will support. The innovations of MEDUWA-Vecht(e) not only contribute to the effectiveness and efficiency of the project as a whole, but also to national and international governmental objectives for the protection of water, soil, air, biodiversity and public health. The project contributes to 7 of the 17 United Nations Sustainable Development Goals. With its source-based approach, MEDUWA follows the European Union Treaty and the European Water Framework Directive. All six goals of the European Strategy for Pharmaceuticals in the Environment were taken into account, as well as goals of the European Green Deal. Furthermore, the project contributes to regional INTERREG-VA Strategic Goals and to growth and employment in the border region.

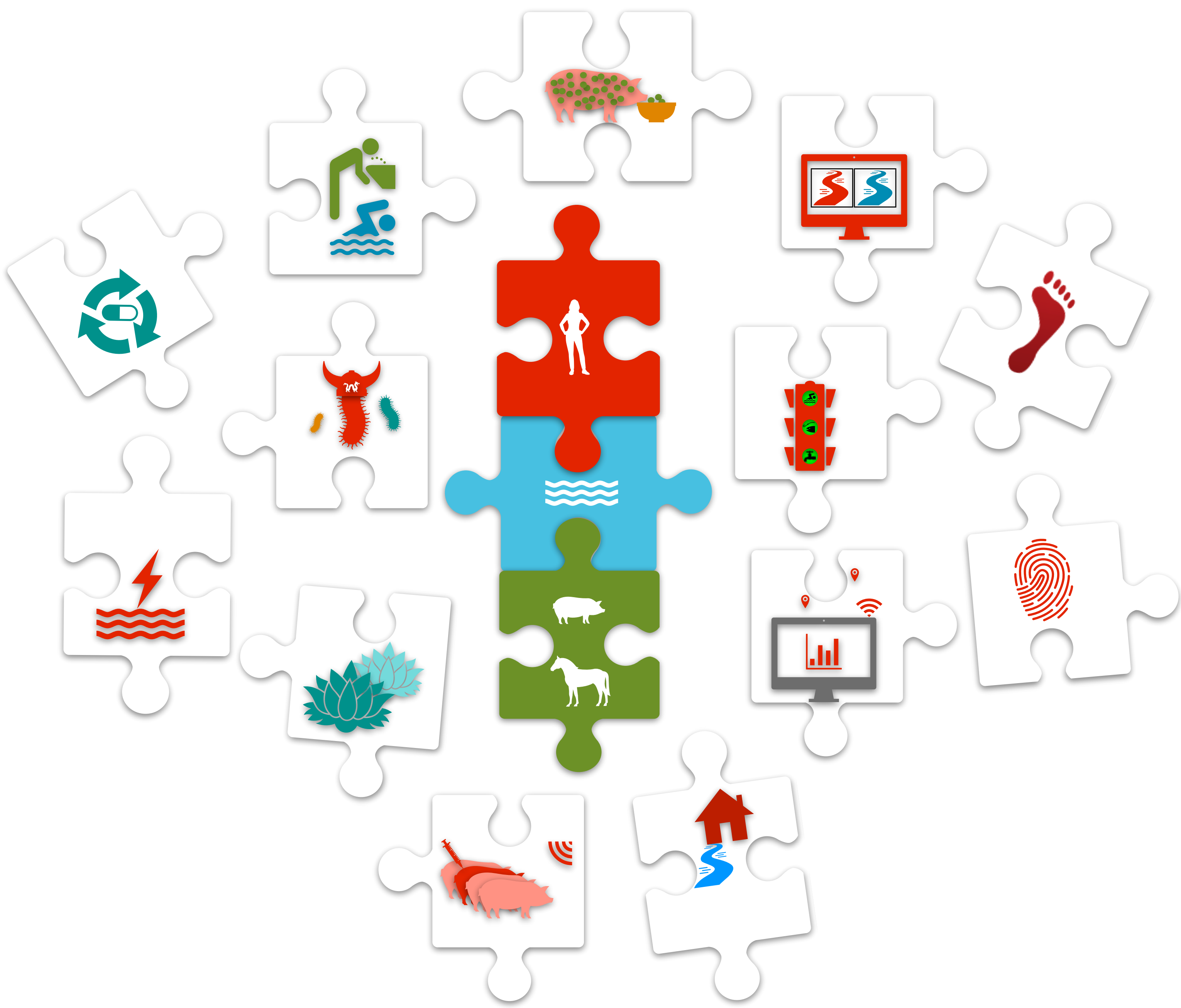
| UN Sustainable Development Goals 2030 | MEDUWA |
|---|---|
| **3. Good health and well-being**<br>- No contamination of air, water and soil | ✓ |
| **6. Clean water and sanitation**<br>- No hazardous chemicals in water | ✓ |
| **9. Industry, innovation and infrastructure**<br>- Clean, environmental conscious industry<br>- More research and development | ✓ |
| **11. Sustainable cities and communities**<br>- Reducing environmental impact<br>- Better waste management | ✓ |
| **12. Responsible production and consumption**<br>- Reduce emissions to air water and soil | ✓ |
| **14. Life below water**<br>- Prevent marine pollution | ✓ |
| **15. Life on Land**<br>- Reduce impact on biodiversity | ✓ |

| European Strategy on Pharmaceuticals in environment 2019 | MEDUWA |
|---|---|
| 1. Increase awareness & prudent use | ✓ |
| 2. Development of biodegradable medicines | ✓ |
| 3. Improve environmental risk assessment | ✓ |
| 4. Reduce wastage & improve waste management | ✓ |
| 5. Expand environmental monitoring | ✓ |
| 6. Fill knowledge gaps | ✓ |
| **European Green Deal 2019** | |

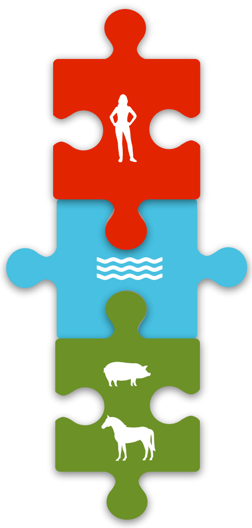
| INTERREG-VA Strategic Goals | MEDUWA |
|---|---|
| **Priority 1** | |
| - Research, technology and innovation | ✓ |
| - Cross-border cooperation between research institutes, small companies and institutes for higher education for development of products and services (pilots and first production), for exchange of technologies and for social and environmental innovation. | ✓ |
| ***Sector Agribusiness/Food*** | |
| - Better quality of products (healthy food) | ✓ |
| - Environmental protection | ✓ |
| - Prevention of formation/spreading of multiresistent organisms | ✓ |
| ***Sector Health & Life Sciences*** | |
| - Prevention of formation/spreading of multiresistent organisms | ✓ |
| ***Sector High-Tech-Systems & -Materials*** | |
| - Development and introduction of new products and services, like watertechnology, sensortechnology, ICT. | ✓ |

# The 12+1 innovations of MEDUWA-Vecht(e)

What is technology today was magic in the past



# Simply complicated



The concept for the MEDUWA-Vecht(e) project was designed by Stichting Huize Aarde.

In 2001, this non-governmental organisation developed the Green Hospitals programme. In this programme, South American and Dutch hospitals worked together. These institutions consider caring for the environment as part of patient care. One of the questions that was raised by hospital pharmacists concerned the fate of medicines such as synthetic hormones, cytostatics and antibiotics after they end up in the environment via the sewers.

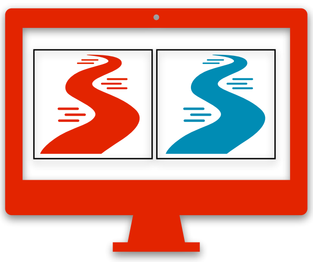
To answer this question, it was necessary to study the subject from many angles. In the meantime, over one hundred students have studied the subject as part of their internships and have put it on the agenda at various institutions. Every institution was recommended to develop measures along the entire life cycle of the product (the responsibility, product or medicine chain), with emphasis on the beginning of the chain.

Ten years later, the MEDUWA concept was born, bringing together various innovators and academics to jointly search for adequate strategies. The aim of MEDUWA-Vecht(e) was to show that a complex and dynamic issue with an ecological and societal impact of global proportions, such as the medicinal environmental cycle, can be addressed in a coherent manner in multiple phases of the life cycle of the medicine by multiple sectors, i.e. human health care, veterinary medicine, environmental management, government, industry, civil society initiatives.

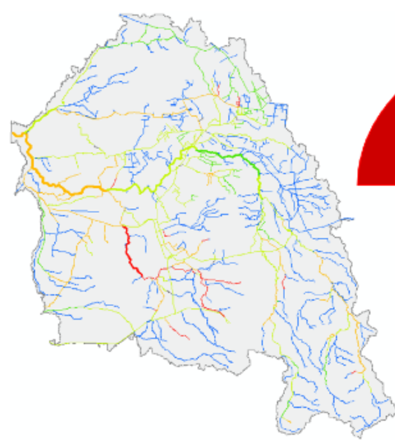
The solution to this problem depends not only on innovation in knowledge and technology. The way in which (semi-)governmental bodies, universities, innovators and other actors communicate and cooperate is also decisive. In practice, this requires inclusive transdisciplinary, cross-sector and cross-border cooperation. Each actor has the knowledge, influence and ability to develop solutions and change processes at their own specific level in the product chain.

The practical implementation of the MEDUWA concept could be brought to a successful conclusion thanks to the close and respectful cooperation of Osnabrück University, The Integrated Assessment Society (TIAS) and EUREGIO.

# Making the invisible, visible

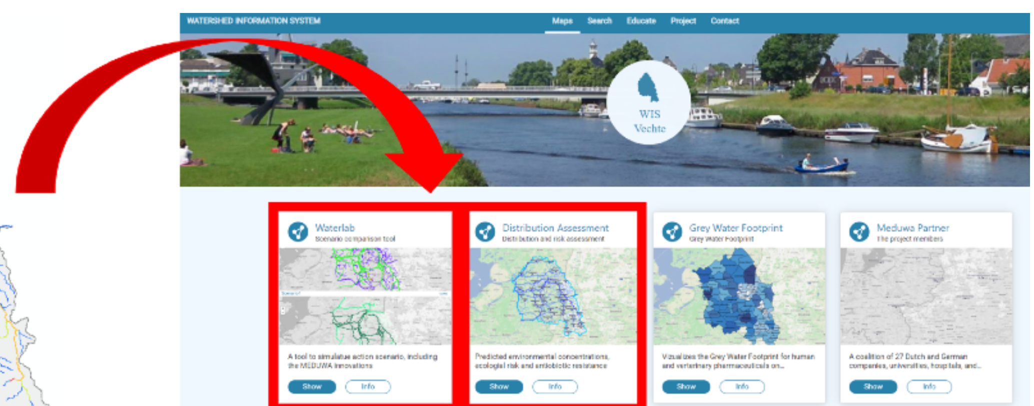


The [Institute of Environmental Systems Research](#) of Osnabrück University, [Geoplex GIS GmbH](#), Wetsus, Radboud University, and University of Twente, pooled their efforts and experience to set up a digital platform for risk assessment for a wider audience, the [Watershed Information System (WIS)](#). The basis of the WIS is the Geography-referenced Regional Exposure Assessment Tool for European Rivers, or [GREAT-ER model.](#)



The aim of the WIS is to visualise and evaluate the complex behaviour of medicines and their potential effects on ecology and the health of local communities with regard to water. This has been assessed under both wet and dry weather conditions. Wetsus analysed the medicines and resistant bacteria (ESBL *E. coli*) in the entire case study area. The model-calculated concentrations of medicines and bacteria were compared with values measured in the samples in order to improve the model. Waterschap Zuiderzeeland (the regional water authority in the Dutch province of Flevoland) provided data on the efficiency of removal by sewage treatment plants.

The results of the modelled scenarios formed an important basis for the risk assessment carried out by Radboud University. In the WIS, the predicted concentration and the ecological risk of 15 medicines for each segment of the Vecht(e) river basin can be retrieved. The selection pressure of antibiotics can also be retrieved for any location.



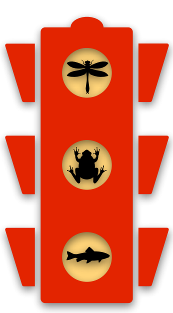

The digital platform is also used by other project partners in the MEDUWA-Vecht(e) consortium to visualise and evaluate the effectiveness of their innovations. The WIS can be used to simulate the potential contribution of each developed measure to reducing the emission of medicines and multi-resistant bacteria for the entire watershed. In this way, the platform is also suitable for communication and decision-making on measures to reduce pollution from medicines.

## Side-effects of medicines in the environment

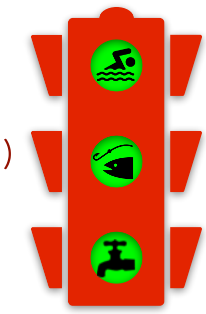
The Human and Ecological Risk Assessment Group of the Radboud University Nijmegen uses large data sets, advanced computer techniques and statistical models to assess the environmental risks of hazardous substances.

The main objective of this research group in MEDUWA was to optimise the environmental risk assessment of pharmaceuticals so that water managers and policy makers are better able to protect the environment and public health. The studies carried out for the Vecht(e) watershed serve as a model for future international risk assessments of medicines in the environment.

In cooperation with the Institute of Environmental Systems Research of Osnabrück University and Wetsus, the group mapped the risks of some medicines in the Vecht(e) River.



For aquatic plants and aquatic animals, the concentrations of some medicines in Vecht(e) water are sometimes too high.



On the basis of current knowledge, the public health risks for people who come into contact with the water of the Vecht(e) via drinking water, sport fishing and swimming are small.

In addition, a literature study has been conducted into the relationship between the antibiotic resistance levels of microbes and antibiotic concentrations in water. The degree of antibiotic resistance of bacteria in surface water is related, among other factors, to the presence of antibiotics in sewage, surface water and sediment. Follow-up research will focus, among other things, on the risks associated with combinations of medicines and biologically active transformation products of medicines.

The results obtained were partially incorporated in the Watershed Information System (WIS) and will be made available from meduwa.eu.

Radboud Universiteit

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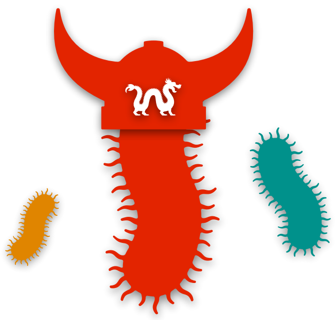
wetsus

# Multi-resistance is also a side-effect



Within the framework of MEDUWA-Vecht(e), Wetsus European knowledge centre for sustainable water technology in Leeuwarden, together with Osnabrück University, analysed and modelled *Escherichia coli (E. coli)* bacteria as well as antibiotic-resistant *E. coli*, in the entire Vecht(e) watershed as an indicator of faecal pollution. Insights into the fate of bacteria in a catchment area can help predict human exposure to (multi-resistant) bacteria, for example during recreational activities in water or via drinking water and irrigation of food crops.

At 25 locations, the surface water of the Vecht(e) and its tributaries was sampled repeatedly. In addition, samples from the outflow of sewage treatment plants and ditches in agricultural areas were taken throughout the basin. The samples were analysed for the presence of *E. coli* by means of cultures. The proportion of the *E. coli* that can produce ESBL or carbapenemase enzymes is also determined. At seven locations, both *E. coli* and the resistant variants were isolated from each sample taken at that location. Concentrations were highest in winter. The GREAT-ER model was used to model concentrations in the various locations.

Photo: Jürgen Berlekamp UOS/IUSF

Based on the *E. coli* concentrations found and modelled, it was concluded that the Vecht(e) watershed does not have water quality that is safe for swimming everywhere. At a number of these bacterially-contaminated locations, bathing takes place on summer days. What this means for public health has not yet been investigated.

The results obtained have been incorporated in the Watershed Information System (WIS) and become available at meduwa.eu.

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## Medicines leave a footprint in water

The Water Footprint is a well known indicator of the volume of water consumed for the production of goods and services. The Water Footprint is suitable for demonstrating water use issues to the general public, the commercial sector, policy makers and decision makers. In addition to the Water Footprint, a tool called the 'Grey Water Footprint' has now been developed. This new concept provides a measure of how much water is needed to reduce the concentration of a pollutant in water to a level that is no longer toxic according to water quality standards. This amount of water depends on the amount and toxicity of a given pollutant in the water.

In the MEDUWA-Vecht(e) project, the University of Twente's Multidisciplinary Water Management research group calculated the Grey Water Footprint of various human and veterinary medicines for the German-Dutch Vecht(e) watershed. The largest Grey Water Footprint from human medicine use in the area was found for the hormone ethinylestradiol, commonly used in the birth control pill: amounting to 16 billion cubic metres of water per year. In other words, it would take 16 billion cubic metres of water per year to reduce the concentration of this substance in the Vecht(e) Basin to non-toxic levels. This hormone originates exclusively from households and 95% for this hormone comes from the Dutch part of the catchment area, due to the higher number of inhabitants and higher usage.

The largest Grey Water Footprint originating from hospitals was found for the antibiotic, ciprofloxacin.

The largest Grey Water Footprint from livestock farming in the catchment area was found for the antibiotic amoxicillin. The results also show that a considerable amount of manure produced in the Vecht(e) region is exported. This means that pollution from veterinary medicines takes place outside the region: 35% of the German and 55% of the Dutch share of pollution is outside the catchment area.

The results of the Grey Water Footprint analysis are visualised in the Watershed Information System (WIS) developed by project partners Geoplex GIS GmbH and Osnabrück University. Interactive maps show the footprint of medicines per municipality, region, hospital or livestock product (dairy products, beef, pork, chicken and eggs). The publications are available at meduwa.eu.

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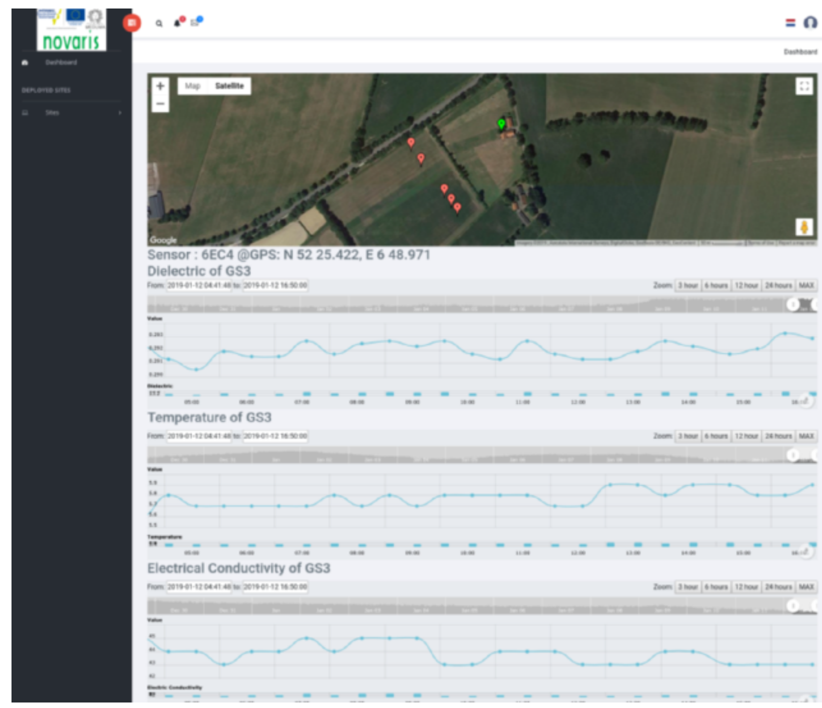
## Remote measurement of the hydrological regime in soil 24/7

Gaining insight into the hydrological regime in soil is not only important for agriculture in order to support green meadows and good yields. Data on soil permeability and groundwater levels are also useful for mapping the distribution of underground water flows containing contaminants such as salts, fertilisers, medicines and pesticides. These data for soils are not easy to obtain. Existing measuring systems are not only expensive, but also difficult to install and the data difficult to interpret.

With the aim of gaining better insight into the hydrological regime in soil, Novaris Orbit Technology BV in Saasveld has developed a new wireless and energy-efficient underground measuring system as part of the MEDUWA-Vecht(e) project. The sensors are entirely buried in the soil and data are transmitted from these. The meadow or field can therefore continue to be used normally; there is no equipment or antenna above the ground. This also makes it possible to place sufficient sensors in a meadow so that an accurate measurement can be obtained for the management of water for an entire plot. All the information from the sensors is transmitted via an underground wireless network to a central point, usually at the farm itself.




Depending on the availability of suitable sensors, data on groundwater quality can be collected in addition to water quantity. The farmer or the water authority can thus determine almost continuously whether there is sufficient water in the soil, whether the permeability of the soil and the quality of the water are good, and also where the groundwater flows to. Irrigation and fertiliser applications can then be better adjusted to soil conditions, and groundwater managers gain better insight into the spread of contamination.

In the MEDUWA project, this wireless measuring system has been tested in several test fields and will be further developed in the coming years.

# Searching for the fingerprint of medicines in the environment 24/7

The start-up InProSens UG develops innovative sensors based on optical measurement technology. These devices can be used to gain direct insights into the composition of both liquid substances and solid materials.

Until now, water samples had to be sent to a laboratory to determine the level of medicines in water, soil and food. There, these samples are prepared using complex methods and then analysed with ordinary laboratory instruments. Analysis results are therefore usually only available a few days after sampling. This also makes the analyses expensive. Moreover, these are only samples. Direct intervention, for example, to adjust the wastewater flows on the basis of the analysis results, is therefore not possible.

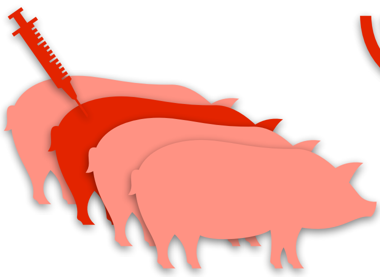
In the MEDUWA-Vecht(e) project, InProSens has focused on developing a measuring device with which liquid samples can be analysed continuously and within a few seconds on site, for example in a sewage treatment plant. In this way, the concentration of pollutants can be observed over a longer period of time.

The sensor system developed is based on the non-destructive, chemical-free principle of optical radiation. The sample to be measured is irradiated by a sensor using light in the near-infrared range. The sample absorbs a characteristic part of the light. The part of the light not absorbed by the sample is reflected back to the sensor, which receives an individual absorption spectrum of each substance, as characteristic as a persons's fingerprint.

The sensor will be ready for use in the chemical industry from 2021. The component of the sensor for measuring very low concentrations of medicines still needs further optimisation. In cooperation with the partners in the MEDUWA consortium, InProSens has already been able to test the sensor in a realistic pilot sewage treatment plant.

InProSens
Innovative Process Sensors

# Monitoring animals 24/7

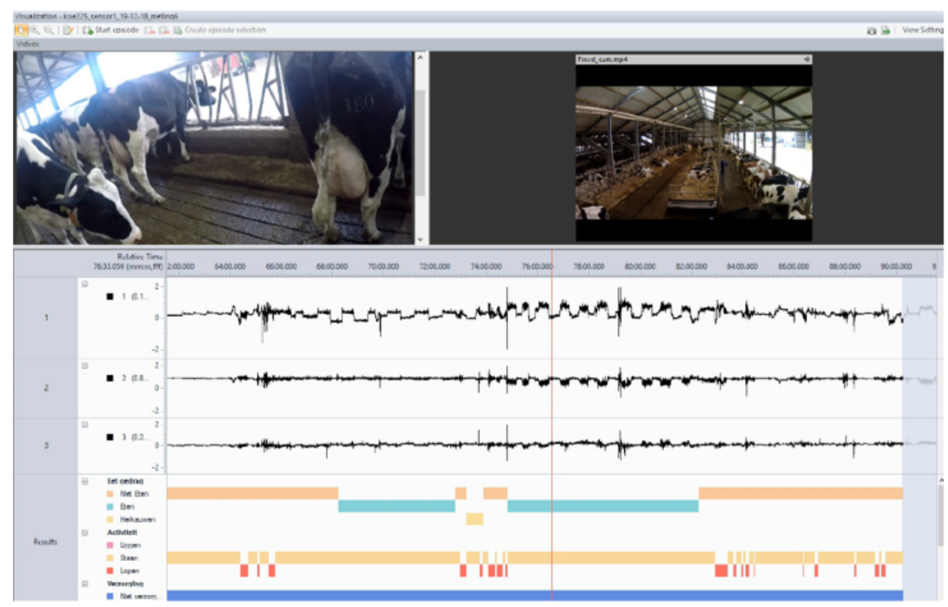


Noldus Information Technology from Wageningen has been developing integrated systems for animal behaviour research since 1989, with the aim of improving animal health and welfare.

With the trend towards larger stalls for groups of farm animals, it is becoming increasingly important to be able to monitor the behaviour, health and welfare of individual animals in those groups. Individual monitoring allows for early detection of disease and rapid targeted responses, thus contributing to a reduction in excessive applications of medication. Individual monitoring also helps to identify animals exhibiting undesirable behaviour, such as feather pecking in poultry and tail-biting in pigs.

Traditional methods of monitoring, such as live observation and video-based manual scoring of behaviour, are subjective and time-consuming. In the MEDUWA-project, a robust and accurate system for automated observation of animals was further developed, allowing multiple types of animal data to be collected. Using ultra-wide-band radio technology, the TrackLab™ system allows real-time individual tracking of large numbers of animals over large areas with high spatial accuracy and a sufficient number of readings.

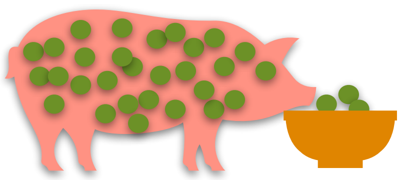
The next step was to increase the system's ability to automatically detect specific behaviours. This worked well: eating behaviour (eating and ruminating) can now be recognised with 95% accuracy. Locomotion including lying down and standing up can be detected with respectively 87% and 81% accuracy.



The ultra-wide-band sensors were developed by project partner Ubisense GmbH in Düsseldorf. Demcon BV, project partner in Enschede, developed a prototype of a body temperature sensor, based on subcutaneous measurement and wireless data transmission. Noldus IT focused on developing the software: a versatile and user-friendly tool for data collection, storage, visualisation and analysis. Together with the sensors and data processing hardware, this has resulted in an integrated solution for livestock research and precision agriculture.

Noldus Information Technology · DEMCON advanced mechatronics · Ubisense

# Reducing antibiotic use with micro-algae



The use of medicines plays a major role in modern animal husbandry. The animals themselves, the quality of the food they provide and the environment suffer from the overuse of medicines, especially antibiotics. Micro-algae can reduce the unnecessary reliance of medicines. Scientific studies show that micro-algae have positive properties and can make a valuable contribution to a healthy diet for humans and animals. Micro-algae are edible, and although they have been on the menu in Asia for centuries, they are still not well-known as a food to Europeans.

The Melle-based company, Microganic GmbH, is a partner in the MEDUWA-Vecht(e) project and a specialist in the production of micro-algae as an ingredient for animal feed and food. Their idea is to use the positive effects of micro-algae to prevent or mitigate the development of diseases using a sustainably-cultivated raw material that is natural and entirely plant-based - a clear advantage over reliance on environmentally-persistent medicines. Micro-algae can be used advantageously in the feed sector for farm animals or pets, but also as food supplements for human consumption. The technical processing of micro-algae in a wide variety of existing standard feeds is generally possible without any problems. In this way, the health of animals and humans can be promoted naturally and easily, and excessive use of medicines can be avoided.


The MEDUWA-Vecht(e) project investigated whether and which micro-algae can positively influence the health of pigs. To this end, selected micro-algae were incorporated into pig feed and fed to the animals over a period of time. German and Dutch scientific institutions and companies were involved in the research to study the effects in the laboratory and in practice. The results of the feeding trial showed that the selected algae indeed had positive effects on the health and growth of the pigs. Further research is needed to find out more precisely how and in which situations the micro-algae can best fulfil their potential to promote animal health.

microganic®

# Innovation in tradition

The Europa Ayurveda Centre (EAC) in Witharen (NL), the institutes of Hygiene and Medical Microbiology of the Münster University Medical Centre (UKM) and Wetsus carried out research into the purifying and antimicrobial properties of plants.

For the MEDUWA study on the antibiotic effect of Ayurvedic plants and plasma-activated water, classical microbiological methods as well as new culture-independent techniques and procedures at cellular and molecular levels, including flow cytometry and polymerase chain reaction (PCR), were applied and further developed by UKM.

In this context, it was investigated whether ayurvedic plants can purify water contaminated by medicines (phytoremediation). It was demonstrated that a set of five water plants is capable of reducing concentrations of medicines such as tetracycline, metformin and erythromycin in the water. What exactly happens to the medicines needs to be investigated further. For example, other variables that can influence the fate of medicines, including natural UV radiation, should be excluded in follow-up research.

According to Ayurvedic health science, plant extracts also have a bacterial-inhibiting effect.

The EAC cultivated 15 different water plants (the Bhima Choorna formula) for this purpose, for which the antibiotic effect on spore-forming, skin, environmental and waterborne bacteria could be clearly demonstrated. According to the UKM, the use of the extracts as a substitute for antibiotics in veterinary and human medicine is therefore conceivable and will now be tested in further studies and projects.


The Bhima Choorna formula will be further developed as a natural antibiotic for animals and humans. In the next phase, randomised, double-blind experiments will be conducted. With this, the Europe Ayurveda Centre hopes to provide an effective solution to the huge problem of antibiotic resistance and the many side effects of current antibiotics. The product is expected to be on the market in 2024.

# Replacing environmentally-persistent medicines

Alloksys Life Sciences BV, AMRIF BV and TDI BV based in Wageningen (NL) are companies developing medicines based on alkaline phosphatase (AP), a non-toxic biodegradable enzyme. AP has the potential to both prevent complications and avoid the use of various side-effects-causing and environmentally-harmful and -persistent anti-inflammatory agents as well as antibiotics.

The companies have been working on the use of AP during major surgical procedures to prevent complications, such as renal failure due to the release of inflammatory substances during and after surgery. AP also prevents the need for long-term reliance on of large amounts of various post-operative medicines.

Supported by the MEDUWA-Vecht(e) project, a clinical study with 1250 cardiac surgery patients was started. In addition, clinical studies were started for the use of AP in kidney transplants and for burn patients, which are also situations where large amounts of medicines are used. Furthermore, a study with COVID-19 patients was initiated, aimed at avoiding the need for ICU admission and the associated need for large amounts of medicines. Aix Scientifics, an experienced clinical research organisation based in Aachen, has supported the Dutch partners in carrying out these trials in various hospitals.

In addition, AP is being targeted at reducing chronic inflammation, which is thought to contribute to conditions such as diabetes, obesity, and neurodegenerative diseases such as Parkinson's disease. In the case of diabetes, the enzyme may prevent use of the environmentally harmful metformin.

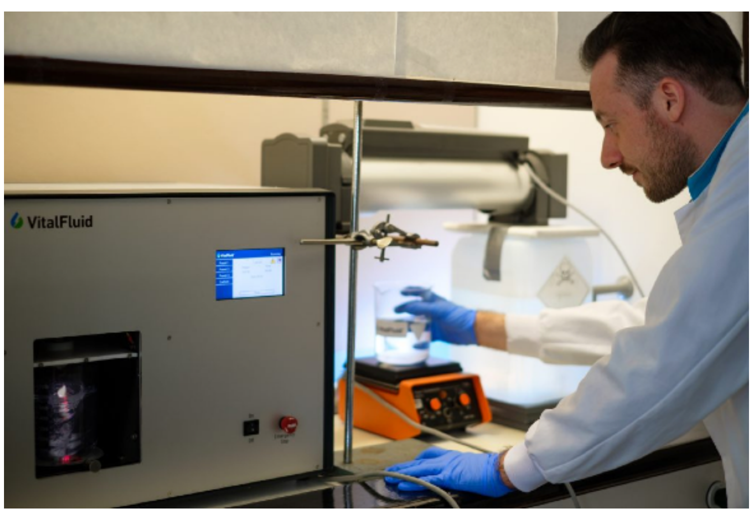
The companies have also conducted a study to reduce antibiotic use in piglets. Disruption of the intestinal barrier system, accompanied by indigestion and diarrhoea, is a common condition in piglets for which antibiotics are commonly used. The use of AP in piglets is expected to remedy this post-weaning syndrome.

Finally, the development of oral applications (pills or capsules) was a major hurdle in making AP treatment possible. AP, if administered orally, needs to be protected from stomach acid.
New sources of AP have also been sought. Currently AP is extracted from the intestines of cows. AP production from genetically-engineered plants is a less expensive alternative which may be applied in the near future.

tournois dynamic innovations bv Alloksys Amrif Dr. Eike G. Fischer Aix Scientifics Contract Research Organisation

# Cleaning water with air

VitalFluid BV from Eindhoven is specialised in plasma technology, an oxidation process that makes exclusive use of air and electricity. Air is brought into a plasma state using electricity and then brought into contact with the water to be treated. Reactive oxygen and reactive nitrogen from the air dissolve in the water and break down the contaminants.




The MEDUWA-Vecht(e) project investigated whether plasma technology could be used to render medicines and micro-organisms harmless at the source before they are discharged into the sewage system. Since the concentration of pollutants is highest here, this is the most energy-efficient means of reducing or eliminating harmful substances. By developing the plasma oxidation technology on a small scale and in modular form, it can be used flexibly at the source for many water purification applications, for example, mobile units that patients can connect to the toilet during treatment with medication at home.

The disinfecting effect of this technique was investigated by the Institutes of Hygiene and Medical Microbiology of the University Hospital in Münster (UKM). The plasma-activated water demonstrated a strong bacterial-suppressing effect in numerous test series and the quantity of living bacteria was minimised. Waterbacteria and physiologically stable bacteria were also killed. According to UKM, the oxidation technique can therefore be used in hygiene processes such as toilet flushing or surface cleaning.

The Molecular Epidemiology Research Lab at the Radboud University Medical Centre in Nijmegen has investigated whether medicines can be removed from water using this technique. On a laboratory scale, it appears to be possible to use plasma-activated water to break down medicines such as cyclophosphamide, diclofenac, metoprolol and paracetamol into a cocktail of hundreds of smaller molecules with reduced toxicity. The remaining level of toxicity is subject of further research. In any case, degradation by plasma-activated water appears more effective than by conventional techniques, such as UV. The technique has already been tested on a small scale with urine from patients. This has given rise to the idea of purifying urine from day care patients before it is flushed into the sewer system. The Radboudumc will install a test unit in the hospital for this purpose.

# Safe water

NX Filtration BV and Saxion University of Applied Sciences in Enschede together with Weil Wasseraufbereitung GmbH from Osnabrück, three partners in the MEDUWA-Vecht(e) project, combined of "brains, passion and skills" for fruitful cross-border cooperation. Together, they took a big step towards introducing a nanofiltration product that removes micro-pollutants from the effluent of sewage treatment plants.

The nanofiltration membrane is a new and specialised membrane developed by NX Filtration. This membrane has an extremely thin selective layer. Water and minerals can pass through this layer, but the pores of the layer are too small for most micro-pollutants. The result is that the micro-pollutants that are still present in the current effluent are trapped by the filter, resulting in clean and safe water. In addition to pharmaceuticals, the nanofiltration process also removes other components of concern such as microplastics and nanoparticles, such as titanium dioxide in paint and sunscreen, that cannot be filtered out or broken down by other treatment technologies such as UV, ozone and activated carbon. Potential applications include not only the treatment of effluent for direct re-use or replenishment of groundwater, but also the direct treatment of surface water to produce water suitable for drinking.


In the MEDUWA-Vecht(e) project, the partners demonstrated the efficiency and effectiveness of this technique at a number of locations in both the Netherlands and Germany. They started at the level of one-day laboratory experiments and progressed to a test bed at the Glanerbrug sewage treatment plant (NL). There, tests were carried out to demonstrate the stable, long-term operation of nano filtration. In the last phase of the project, long-term tests were performed with several versions of the nanofiltration membrane under different process conditions at various sewage plants in the Vecht(e) catchment area. Follow-up research focuses on optimising the processing of the remaining concentrate.

## Collective or individual water treatment

A central role of Waterschap Zuiderzeeland, the Water Authority of the Dutch province Flevoland, in the MEDUWA-Vecht(e) project was research into the possibility of removing medicines from the effluent of individual treatment systems for domestic sewage in regions without sewage systems.

With this study, the Water Authority has shown that it is possible to remove medicines with individual treatment systems. The aim was and is to initiate a dialogue on the benefit and necessity of these systems, and the suitability of various individual treatment techniques. A good example of this is the MEDUWA-study into small-scale application of plasma-activated water technology for the oxidation of medicines and (multi-resistant) micro-organisms.

In addition, Waterschap Zuiderzeeland, together with five other Water Authorities, has generated data on concentrations of medicines in the inflow to and effluent from sewage treatment plants. These data were used in the GREAT-ER model and the Watershed Information Systeem, WIS, see also on page 11. This digital information system can be used by water authorities to visualise the effect of sewage water treatment and other measures on the watershed.

# MEDUWA-Declaration

According to the 2019 fitness check of the European Water Framework Directive, synthetic chemicals (incl. pharmaceuticals) and their impacts on the environment and human health still receive insufficient attention in the Framework Directive and all other related European Directives. In order to promote the approach to addressing pharmaceuticals and multi-resistant bacteria in the environmental cycle, the MEDUWA Declaration below was made. Since February 2020, project partners and stakeholders have signed this declaration on behalf of their organisation or in a personal capacity.

**Would you like to sign the declaration below?**
**Please send your name and address to post(at)meduwa.eu**

The undersigned declare that:

1. This issue of the medicinal environmental cycle should be subject to a combined health policy by both the human and veterinary health sectors, the One Health approach;

2. It is important that the water, human, veterinary and animal agriculture/aquaculture sectors cooperate in order to solve the issue to the extent possible at its source;

3. During the education and training of those who prescribe medicines more emphasis should be placed on the topic of the medicinal environmental cycle;

4. Policies and legislation should place more emphasis on the production and use of environmentally friendly medicines;

5. The contamination of surface, ground and drinking water, soil, food and air with these chemical and biological contaminants must be considered a public health issue, and, in accordance with the precautionary principle, be avoided;

6. in accordance with the EU Polluter Pays Principle, in all EU Member States environmental quality objectives should be integrated into policies concerning agriculture, human and veterinary health in order to contain societal costs;

7. Also regional and local authorities need to integrate policies on environment, agriculture and human/veterinary health and facilitate pilot projects to this end;

8. All relevant EU research and development funding programmes should give more priority to the development and upscaling of innovative source-based solutions to these issues.

Finally, we thank the stakeholders for their interest, critical questions, support and inspiration.

Meeting of project partners and stakeholders at the University of Osnabrück, 2018.

For more information and updates: meduwa.eu

Contact: post(at)meduwa.eu