

Workshop Pandemie en RWZI

Bilthoven, 20-01-2011

Synthesis

The topic of the workshop provides an example of cross-disciplinary environmental toxicology, where the domains public health and environment interact. The projections for the Dutch water chain, from waste water to drinking water, show what information is needed to decide on precautionary measures.

The following conclusions were supported by current data:

- Epidemics with a low infectivity and/or a low level of secondary infections are not likely to affect proper functioning of STPs. Epidemics with a high infectious flu and/or a high level of secondary infections are more likely to do so.
- STPs are not designed to eliminate toxic chemicals. Normal use of medication provides for a base level of contamination. Impact of antibiotics on STP functioning will mainly lead to additional increased loads of BOD/COD, microbial parameters, and nutrients.
- Although an intensified use of medication may lead to reduced water quality (based on the precautionary quality standards for drinking water), the acute risk for public health is negligible. In view of the seasonal pattern of an epidemic event, chronic risks of exposure above water quality standards are not likely. In case of STP failure, control measures for intake of drinking water would primarily respond to other water quality parameters.
- It seems justifiable to accept that an increased use of antivirals will result in a reduced use of antibiotics, and hence overall in less risk for STPs.

General

The meeting was attended by Mark Montforts (chair), Monique van der Aa, Aura Timen and Lonneke van Leeuwen from RIVM, Thomas ter Laak from KWR, Heike Schmitt from IRAS, Wim Wiegant from Royal Haskoning, Andrew Singer from the UK Centre for Ecology and Hydrology, Sybrand Landman from the ministry of VROM, Cora Uijterlinde from Stowa, Rob van Doorn from Waterschap Vallei en Eem, Peter van der Wiele from Waterschap Regge en Dinkel, Elbert Majoor from Waterschap Velt en Vecht, Stefan Kools from Grontmij/Aquasense and Alfons Uijtewaal from Stichting Huize Aarde.

Mark Montforts welcomed all participants and opened the workshop.

Aura Timen – Influenza pandemic: the use of antivirals

Aura Timen gave an introduction on the influenza virus and the history of influenza pandemics in the 20th century. She showed data on clinical attack rate and made a comparison between

seasonal influenza and a pandemic (a pandemic is more widespread and has the potential to disrupt society), concluding that not all pandemics behave the same.

Aura showed data on the new H1N1 virus, a recombinant of four other viruses derived from birds carried around by pigs. Next, she reported on the response of the Dutch authorities to the occurrence of the new H1N1 virus, which created a stockpile of antivirals (5 million courses, assuming a clinical AR of 30%). After a few weeks the prescription of oseltamivir was strongly restricted based on fear of causing viral resistance.

Conclusions on the course of the new H1N1 virus epidemic:

- Incidents trigger an increase in consumption of antivirals.
- The prescription behaviour of general practitioners and public health services was according to the guidelines.
- There was proper communication on indications for prescribing antivirals.
- There was a restricted demand for antivirals from the public.

Questions were asked on what is typical for the seasonal flu versus the new H1N1 virus epidemic? Aura answered that seasonal flu peaks during autumn and winter. For the new H1N1 virus, ongoing transmission was observed during the summer. This caused fear for the occurrence of enormous peaks during autumn.

Further, it was asked whether there is a difference between countries in patterns in the occurrence of seasonal flu. Aura answered that differences in countries are indeed observed, i.e., what is typical in Western Europe is not typical for Southwest Asia. These differences are climate determined.

Caroline Moermond / Mark Montforts – Tamiflu in the environment

Mark Montforts gave an introduction on how environmental risk assessment (ERA) of pharmaceuticals is performed in general, followed by a more detailed review on the ERA for oseltamivir.

The ERA has two phases: In the phase I assessment a predicted environmental concentration (PEC) is calculated. In case this PEC value exceeded the trigger value for phase II assessment. In the phase II assessment the PEC can be refined and predicted no effect concentrations (PNECs) are determined for various organisms based on laboratory tests.

For oseltamivir, the ERA was not based on pandemic use of the substance, although this possibility was mentioned. When 30% of the population uses oseltamivir at the same day, PEC values for surface water can reach levels of 21 µg/L, exceeding the trigger value of 0.01 µg/L.

However, based on a pandemic use pattern (a high peak in use of the medicine during a short period of time) and the physico-chemical characteristics (persistent in the environment;

almost no degradation in the SPC) of the substance, it can be doubted whether the assumptions in the PEC calculations based on default values are applicable for the ERA of oseltamivir. Monitoring and higher tier modeling data show concentrations up to 460 ng/L.

When the PEC value of 21 µg/L was compared to the PNEC values, no risk was expected for the surface water and groundwater compartment from direct exposure to oseltamivir.

However, for the sewage treatment plants, risks cannot be excluded.

For the risk assessment for drinking water no guidance is given by the EMA. However, when the calculated concentrations of oseltamivir are compared to the human toxicological effect values, the margin of safety is large enough not to expect effects.

Questions were asked on the possibilities to remove oseltamivir from surface water. It was explained that oseltamivir cannot be removed from water by carbon filtration based on the physico-chemical properties of the substance.

Further, it was asked why the data from the original ERA for oseltamivir are incomplete according to the current guidelines. Mark explained that the original ERA was performed before 2006, when the most recent EMEA guideline came into force.

Thomas ter Laak – Geneesmiddelen in de Rijn

Thomas ter Laak showed the current status on pharmaceuticals in the river Rhine. Nine locations along the Rhine were monitored monthly between 2002 and 2008 (2003 excluded). Analyses were performed for 127 pharmaceuticals and endocrine disruptors. The 20 substances found most often were studied in more detail.

Concentrations varied between 0.01 and 1 µg/L. Anthropogenic pressure tends to increase with the course of the Rhine (Lobith is more densely populated than Basel). Most substances do not show significant temporal trends, however the loads varied during the year. Seasonal variations in concentrations of pharmaceuticals due to seasonal variations in use were observed.

Thomas showed an alternative PEC calculation for oseltamivir, resulting in a PEC surface water of 6 µg/L.

It was asked how many chemicals were found at the same time at the same place. Thomas answered this was approximately 20. Further, it was asked whether Thomas tried to relate the suspended matter content in the water to the measured concentrations. This was not tried because the pharmaceuticals found were not that hydrophobic that suspended matter content has a large influence on concentrations in the water.

Discussion evolved on the possibilities to link monitoring of pharmaceuticals to pharmacists. Some data are available, showing quite big differences between countries. These are probably caused by differences in policy.

It was noted that higher concentrations were reported after rainfall. This could be caused by discharge of untreated sewage.

Since oseltamivir is a pro-drug, it goes into the environment in essentially inactive form. However, it can easily be reactivated by bacteria and therefore, not 75% but 100% enters the environment. This influences the presented PEC calculation.

Heike Schmitt – Antibiotics in the WWTP environment

Heike Schmitt showed how to model antibiotics at a sewage treatment plant and watershed during a pandemic.

First, exposure modelling is needed. In order to do this, you have to find out which antibiotics would be used during a pandemic and which proportion of the antibiotics is excreted in active form. Next, you model the ecotoxicological effects, starting with bacteria. Because very little information of sensitivity of sewage sludge bacteria is available, Heike used MIC values of human pathogens as surrogate. Species sensitivity distributions (SSD) were used to model the effect of antibiotics on STP bacteria. Next, the SSDs were used as input for the toxic pressure model in order to identify the potentially affected fraction. The analyses showed that the effects of antibiotics on the STP depended on viral infectivity. On average, 20% effect was expected. However, adaptation was observed.

The STP is already a hotspot for antibiotic resistance. For example, resistance was found in STP of pharmaceutical production plants.

Heike concluded that in case of low viral infectivity, no ecotoxicity risk is expected. However, when viral infectivity increases, a higher fraction of the species in the STP becomes inhibited, causing risk to river stretches.

Heike was asked to give a further explanation on “high infection rate”. Heike explained that the infection rate is the average number of persons one infects when one’s ill. A R0 of 2.3 is considered medium viral infectivity.

The possibilities of combining the modeling techniques Heike presented and monitoring data in STP influent were discussed. It seems useful to combine these.

Wim Wiegant – Pandemic disease and the WWTP

Wim Wiegant explained how a nowadays Dutch STP works. There are different types of bacteria present in different places in the STP. Important groups are phosphate accumulation bacteria, nitrifying bacteria, anammox bacteria, acetogenic bacteria and methane bacteria, which all have their own role in the STP. These groups have low growth rates, specialized conversions and a low species diversity, causing vulnerable conversions and a relatively low recovery rate.

In case of a pandemic disease, an increase in wastewater concentrations of antibiotics and antivirals is expected. For antibiotics, no general conclusion on effect on the STP can be drawn. Some have more effect than others, and there are large differences in persistency.

Anammox bacteria might be affected. However, high inhibition of pollutant removal in the STP is not likely to occur.

Antivirals have a low effect on nitrification; other effects are not known. However, degradation is very slow. Inhibition of pollutant removal in the STP due to antivirals is very unlikely to occur. Wim concludes that the STP is resistant against many attacks and that with re-inoculation, rapid recovery occurs: there seems little reason for panic.

Andrew Singer – The UK experience. How influenza pandemic control can lead to unpreparedness: modeling the ecotoxicity of pharmaceutical usage

Andrew Singer showed the UK experience of the 2009 new H1N1 flu pandemic: "The solution to pollution is dilution".

Model estimates on water quality in the UK were made on a reach by reach basis. A mass balance of the inputs to the reach was made and new concentrations at the end of the reach were calculated allowing for degradation on the compound of interest. The output of the model was in GIS format. General conclusions are that:

1. A mild pandemic with a low rate of secondary infections is not projected to result in problems for STPs or most UK rivers.
2. A pandemic with an infection rate $> \sim 2.0$ is likely to pose operational challenges to sewage works which could result in the release of untreated sewage into receiving rivers.

Priority research is to determine empirically the vulnerability of sewage works, to assess the short and long-term risks to widespread antiviral and antibiotic release in the environment and to empirically determine vulnerability of drinking water to contamination.

There is a website on pandemic usage of pharmaceuticals: www.prepare.org.uk

A remark was made on the low number of STP breakdowns: only 6 were reported in the last 16 years. How does this relate to the additional resource Andrew proposes? Andrew explains that discovering/preventing catastrophes is not the only goal; preventing a decrease in functioning of the STP is also important.

Discussion/reflection

- For the STP there seems to be no reason for panic since there is overcapacity, however, the strategy is to be ahead of trouble.
- In case of a pandemic, there are possibilities to restore the STP capacity by re-inoculation.
- Exceedance of drinking water standards is not necessarily a health threat.
- Currently, we are not aware of the potential effects of pandemic use of antibiotics. Potentially 40% of our water stretches is at risk, meaning that more than 5% of the species in these water stretches could be affected. It is unclear what this risk means in practice.

- How should we spend our resources? A difference is made between long term planning and a short term event. In case of a short term event, which disrupts society, uninhibited functioning of the STPs may not have priority.
- There is equilibrium between the use of antibiotics and antivirals: when antivirals are used in the treatment of flu, the use of antibiotics decreases. With today's knowledge, we consider antivirals a far smaller ecological danger than antibiotics.
- Industry is searching for "green" antibiotics. However, it is very difficult to find new antibiotics, let alone "green" ones.
- There should be more communication between the water boards and research institutes in order to combine monitoring results with effects modelling.

Follow-up

The following data gaps were identified. Both strategic and operational water quality management would benefit from further research on the mentioned knowledge gaps.

- Effect assessment based on laboratory single species data appears to be predictive for laboratory community testing. It is unclear if these data also apply to complete waste water treatment systems including the different aerobic and anaerobic processes. It is not clear if a predicted affected fraction of species equals the same fraction in performance. In theory, if 10% of the bacterial species would be affected, the complete process could be stopped. As a consequence, there is uncertainty about the magnitude of impact on water ecosystems at a given use rate of human drugs. Research into the robustness of Dutch STPs is recommended.
- Normal use of medication provides for a base level of contamination. There is no communication between research, STP operators and water boards about current potential impacts on STP performance due to a lack of awareness and a lack of data.
- There is uncertainty about the buffer capacity of Dutch STPs, for every step (anaerobic – anaerobic).
- The predictions for epidemics and water quality were not based on Dutch watersheds. Assumptions about development of an epidemic, prescription behaviour of medication (differences between EU member states are large), STP types, water temperature and water flow rates are critical parameters in the modelling.

The results of the workshop will be rewritten into a Dutch manuscript for H2O.