Evaluation report

for medicinal products for human use

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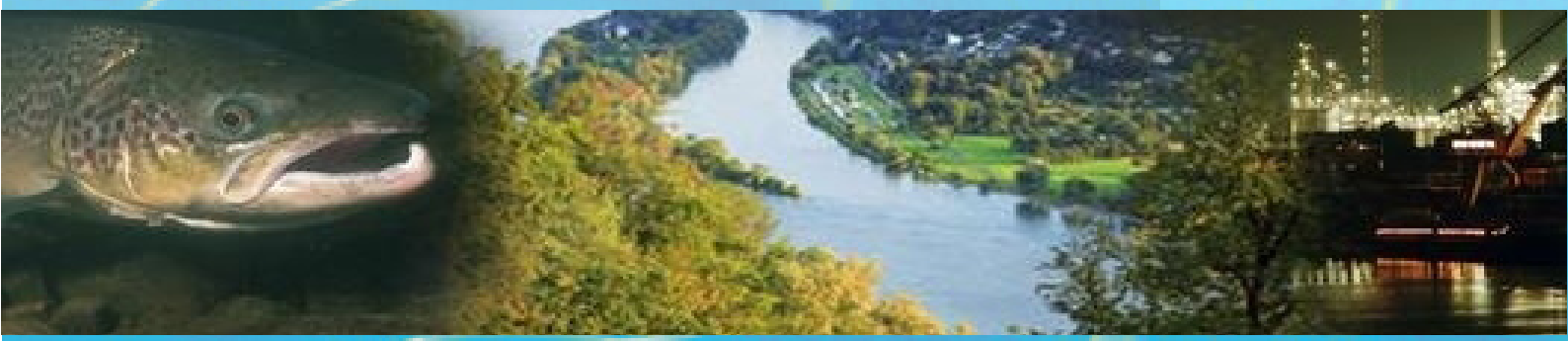

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1. Introduction

Medicinal products for human use are a vital part of our life. They consist of biologically active substances which either reach municipal wastewater due to inappropriate disposal via the toilets or after use as persistent parent substance or as transformed product excreted with urine or faeces. Annually, large amounts of a great variety of agents are being consumed. In Germany, for example, over 30,000 tons of medicinal drugs are consumed in form of 2,500 active ingredients. In Switzerland, the average consumption of the top 40 medicinal products for human use amounts to about 100 mg/person/day (Swiss data). In the Netherlands, the consumption of medicinal products for human use is expected to rise by 20 % by 2020. Due to the high consumption and the stability of these substances it is not surprising that these substances may be detected in surface waters, in groundwater and partly in drinking water. Therefore, it is appropriate to pay attention to the group of medicinal products for human use when evaluating water quality. Medicinal drugs have been developed as agents which may even have an effect in comparatively low concentrations (< 1µg/l).

The following statements are based on information derived from the substance data sheet on medicinal products for human use.

2. Problem analysis

In surface waters, agents of medicinal products for human use are constantly detected in concentrations of few nanogrammes per litre (ng/l) to some microgrammes per litre (µg/l). All depending on the pharmaceutical agent, concentrations vary considerably and depend on different factors such as the amounts consumed, transformation in the human body, elimination in wastewater treatment plants, degradation and dilution in surface waters, mobility in the aquatic phase. Of the four proposed agents of medicinal products for human use: bezafibrate (reducing cholesterol), sulfamethocazole (antibiotics), carbamazepine (anti-epileptic drug) and diclofenac (analgesic and anti-inflammatory drug) the latter two are detected in comparatively high concentrations in the main stream of the Rhine and its tributaries. Therefore, these two substances are suitable indicator substances for the strategy to be developed by the ICPR.
The highest concentrations are found in

- Those tributaries to the Rhine with a high share of (biologically) treated municipal wastewater
- The lower section of the Rhine (Delta Rhine).

The following statements apply to water quality:

- The highest concentrations of some agents of medicinal products for human use detected in the Rhine area are above the proposed environmental quality standards derived according to the rules of the WFD and in the scope of some numerical values, such as concentrations, at which these substances are not expected to have any impact on the environment (PNEC) or the IAWR value of 0,1 µg/l. So far, the Rhine bordering countries have not passed any environmental quality standard for pharmaceutical agents.
- Pharmaceutical agents are found in the raw water of drinking water plants and are partly even detected in drinking water. This particularly applies if river bank filtration is not followed by any further treatment (e.g. activated carbon treatment). This is above all true of the downstream region of the Rhine. However, the amounts of pharmaceuticals liable to be absorbed via drinking water are distinctly lower than the therapeutic doses administered.

The four pharmaceuticals considered are largely detected in the Rhine catchment area. Due to the existence of these pharmaceuticals and of mixtures which might contain these as well as other substances, undesired effects may produce in non target organisms which might not be pointed out beforehand, e.g. within the licensing procedure. Apart from detrimentally impacting aquatic organisms in the Rhine tributaries, the production of drinking water from Rhine water is interfered with. Following the reduction obligation, cost efficient measures are required to reduce the pollution of waters by pharmaceuticals.

3. Analysis of pathways

Mostly, pharmaceuticals reach the municipal wastewater via the wastewater of households and factories immediately after having been applied. Via the combined sewer overflow, during rainfall, a small percentage (about 1 – 3 %) of this municipal wastewater flows directly into surface waters. Also, wastewater from households not connected to the municipal sewer (about 1-2 %) is directly flowing into the surface waters. But more than 95 % of the municipal wastewater flows into wastewater treatment plants. The extent of elimination of a substance in present wastewater treatment plants depends on the substance: bezafibrate e.g. is being comparatively well eliminated, carbamazepine is not being eliminated. A broad variety of pharmaceuticals for human use is constantly detected in the outlets of municipal wastewater plants in concentrations distinctly above 1 µg/l. Thus, urban wastewater treatment plants are a main pathway of input of medicinal products for human use and of their transformation products into surface water bodies. For individual agents, certain emission sources, such as hospitals (e.g. antibiotics, radiological contrast substances) or pharmaceutical works (production of active material) may be important.
As far as the input via urban wastewater treatment plants and incidence in waters are concerned, medicinal products for human use are representative of a number of further substances, such as food additives (e.g. artificial non-sugar sweeteners), cleaning agents, cosmetics, natural and synthetic oestrogens and biocides used in private households.

Table 1: Application of a simple model to calculate loads and concentrations of the four medicinal products for human use in question. Reference for substance model [Ort et al., 2009. Environmental Science and Technology, 43(9)]

Substance / Monitoring station	**Concentration (average value)**		**Load (average value)**	
	ng/l **measured**	ng/l **modelled**	kg/a **measured**	kg/a **modelled**
Bezafibrate				
Weil / High Rhine	11	3	410	100
Mainz / Main	18	25	880	625
Lobith / Lower Rhine	34	17	2.386	1.160
Carbamazepine				
Weil / High Rhine	50	27	1.350	900
Mainz / Main	110	207	5.270	5.025
Lobith / Lower Rhine	88	131	6.175	9.210
Diclophenac				
Weil / High Rhine	24	11	380	370
Mainz / Main	57	100	3.000	2.280
Lobith / Lower Rhine	57	60	4.000	4.185

Substance / Monitoring station	Concentration (average value)		Load (average value)	
	ng/l measured	ng/l modelled	kg/a measured	kg/a modelled
Sulfamethoxazole				
Weil / High Rhine		14	400	460
Mainz / Main	22	115	900	2.700
Lobith / Lower Rhine	40	71	2.807	4.975

The model is based on numerical consumption indications for pharmaceuticals in the Rhine bordering countries (converted to the Rhine catchment) and includes transformation (metabolisation) in the human body and average decomposition in a wastewater treatment plant. The model is sufficient for predicting orders of magnitude of the concentrations and loads of the pharmaceuticals concerned.

4. Possible measures

To minimize the input of medicinal products for human use, emission reduction measures can be taken at different levels:

- Measures at the source;
- Information of the public
- Treatment of split wastewater streams;
- Centralized measures in wastewater treatment plants;
- Adaptation of monitoring programmes.

In the following, the potential measures are developed more in detail.

Measures at the source

- Reduction of the pollution of water bodies by:
  - Enhanced environmental impact assessment during licensing;
  - Information on appropriate disposal;
- Reduction of residual pharmaceuticals in domestic waste and wastewater by:
  - Improved patient compliance (in Germany: above all, patients of general practitioners);
  - Adapted size of packages;
  - Improved possibilities for individual delivery by pharmacies and practitioners
  - Legally embodied obligation of pharmacies to collect expired pharmaceuticals.

Information of the public

The public, including particularly the personnel of health institutions – practitioners, pharmacists, nursing staff as well as patients will be informed about the appropriate disposal (e.g. by information on the package) and about the relevance of certain pharmaceutical agents for the environment and their impact on drinking water production.

Decentralised measures – treatment of split wastewater streams

Depending on the substance, hospitals and other health institutions may relevantly contribute to the loads of medicinal products for human use transiting by wastewater treatment plants before reaching the surface waters. The following measures can be taken into account in order to minimize these loads:

- Information on environmental relevance and appropriate use and disposal of certain agents of medicinal products for human use;
- Organisational measures of disposal: E.g. use of urine collecting bags;

- In specific situations use further treatment procedures to remove pharmaceutical residues (e.g. activated carbon, ozonisation) from the wastewater of split streams originating from certain departments or an entire hospital; e.g. if it is proven that a large share of the pharmaceutical load of a wastewater treatment plant originates from a hospital or nursing home.

Also, industrial and commercial production of pharmaceuticals for human use in the pharmaceutical industry may lead to large pollutant load inputs. The following measures may be taken into account in order to minimize these inputs:

- Organizational measures, such as „good housekeeping“;
- Use of further procedures to eliminate micro-pollutions
- Optimization of production processes

Centralized measures in urban wastewater treatment plants

The use of further treatment procedures to remove micro-pollutions (ozonisation, activated carbon) will increase the elimination performance of wastewater treatment plants. The estimated 3.200 wastewater treatment plants in the Rhine catchment dispose of a total volume of at least 98 million population equivalents. 191 of these wastewater treatment plants (that is 6 % of all wastewater treatment plants) dispose of a total volume of more than 100.000 population equivalents. These wastewater treatment plants dispose of more than half of the entire treatment capacity (54 %) in the Rhine catchment[1]. If these 191 wastewater treatment plants were extended by the afore mentioned further treatment procedures, the input of medicinal products for human use (and of many other organic micro-pollutants from urban wastewater treatment) into the Rhine could be reduced by at least 30 %. This would distinctly reduce the contamination of the downstream section of the Rhine and grant improved drinking water protection along the main stream of the Rhine.

The extension of the largest plants could be controlled by formulating minimum emission requirements or by the States in the Rhine catchment creating incentive systems.

In individual cases, an extension of small to average wastewater treatment plants (10.000 to 100.000 population equivalents) could be envisaged which would regionally improve the ecological/chemical status of the Rhine tributaries. Furthermore, due to the large number of plants, the improvement of the treatment performance of small/average treatment plants has a positive impact on the protection of drinking water resources in the Rhine catchment.

Adaptation of monitoring programmes and systems of assessment

- Based on an assessment of the environmental relevance resulting from substance balances, simple model estimations, eventual indications resulting from licensing procedures and comparable methods[2].
- Based on the results of new analytical research methods[3]
- Taking into account agents of medicinal products for human use and their relevant metabolites when EU Member States assess the ecological and chemical status of

[1] Report to the European Commission on the results of the survey according to Directive 2000/60/EC of the European Parliament and the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (article 15(2), 1st indent); - Part A = Overriding Part)
State: 18.03.05, Coordination Committee Rhine 2005 (CC 02-02d rev. 18.03.05).

[2] As e.g. Ort et al. (2009). Environmental Science and Technology 43(9); Keller et al. (2007). Environmental Pollution. 148; Reemstma et al. (2006) Environmental Science and Technology 40(17)

[3] Singer, H., Huntscha, S., Hollender, J., Mazacek, J. 2008. Multikomponenten-Screening für den Rhein bei Basel. Report of the Eawag, Dübendorf, Switzerland

waters within the framework of the Water Framework Directive and within the framework of the Swiss legislation on water protection.
- With a view to assessing the ecological/chemical status and to protecting drinking water resources, binding quality criteria must be derived on an appropriate institutional level.

5. Conclusion

Summary of the most efficient measures to be further elaborated and examined.

- **Measures at the source** aimed at reducing residues of pharmaceuticals in the wastewater of households and factories and at achieving a reduction of water pollution by extended environmental impact assessment when licensing drugs
- **Information of the public** on the appropriate use and disposal and on environmental relevance and the impact of medicinal products for human use on drinking water production in the Rhine catchment.
- **Decentralized measures:** Treatment of water or split wastewater streams in production units or health institutions directly discharging into surface water bodies or indirectly discharging through wastewater treatment plants and contributing with a substantial part to the load in these wastewater treatment plants.
- **Centralized measures:**
  The experience made in wastewater treatment plants, in which further treatment procedures are used to remove micro-pollutions (e.g. ozonisation, activated carbon) must be collected and interpreted in order to be exploitable for future decisions. Centralized measures taken in a very limited number of urban wastewater treatment plants may e.g. lead to a 30 % reduction of inputs of medicinal products for human use. These measures might also contribute to reducing a broad range of other micro-pollutions from urban wastewater in the Rhine catchment.
- **Adapt monitoring programmes** based on simple model estimations, eventual indications from licensing procedures and comparable methods or based on the results of new analytical research methods
- **Extend the list of priority substances:** Propose selected medicinal products for human use for the candidate list of priority substances of the Water Framework Directive (WFD)
- **Adapt assessment systems:** Take into account medicinal products for human use when assessing the ecological and chemical status of water bodies in the Rhine catchment.