Ministerie van Verkeer en Waterstaat

Directoraat-Generaal Rijkswaterstaat

RIZA Rijksinstituut voor Integraal Zoetwaterbeheer en Afvalwaterbehandeling

Humane en veterinaire geneesmiddelen in Nederlands oppervlaktewater en afvalwater

RIZA rapport 2003.023

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Humane en veterinaire geneesmiddelen in Nederlands oppervlaktewater en afvalwater

een screening in 2002

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Summary

Several studies have been published outside the Netherlands, especially in Germany, showing the presence of pharmaceuticals in both surface and wastewater. For this reason, this survey was conducted in 2002 to establish the occurrence of pharmaceuticals in the aquatic environment of the Netherlands. No data were previously available on this subject.
To identify the presence of human and veterinary pharmaceuticals in Dutch surface waters, measurements were taken both in the major lakes and rivers (such as the Rhine, the Maas and the Ketelmeer) and in regional surface waters. Attention focused not only on the occurrence of human and veterinary pharmaceuticals in the aquatic environment, but also on possible sources of emissions. Accordingly, samples were taken of a number of types of wastewater: domestic wastewater from a residential area, influent and effluent at sewage treatment plants, and wastewater from hospitals, pharmaceutical plants and fish farms. The study did not examine surface run-off and leaching of veterinary pharmaceuticals from manure produced by intensive animal husbandry as a possible emission route into surface water because no suitable chemical analytical methods were available for the measurement of pharmaceuticals in the solid fraction of environmental samples. On the other hand, several new chemical analytical methods were developed to permit the measurement of pharmaceuticals (especially veterinary pharmaceuticals) in the liquid fraction of environmental samples. In addition, an effort was made to obtain a reliable estimate of the risks to the environment by conducting a study of the literature on possible adverse effects of pharmaceuticals on aquatic organisms.

Selection of pharmaceuticals

Approximately 12,000 human and 2,500 veterinary pharmaceuticals are currently permitted in the Netherlands. Each of them is composed of an active ingredient (or therapeutic moiety) plus various auxiliary substances used to make the drug convenient to take or administer in uniform dosages. Because of their biological activity, the active ingredients are of particular importance. In the Netherlands, around 850 different active ingredients are used in human pharmaceuticals, and some 200 in veterinary pharmaceuticals. For the purposes of this survey, around 100 active ingredients were selected. The selection process took account of available chemical analytical techniques, the environmental concentrations reported in studies conducted outside the Netherlands and, where possible, the estimated risks to the aquatic environment. The selected categories of pharmaceuticals included antibiotics, coccidiostatics, analgesics, x-ray contrast media, drugs used to treat coronary vascular disease, antineoplastic drugs and antiepileptics. In almost every case, monitoring focused on the active ingredients and no effort was made to detect their metabolites.

Analyses

Chemical analytical methods of detection in aquatic environments are available for only a small percentage of the human pharmaceuticals used in the Netherlands and their accompanying metabolites. At the time of the study, no chemical analytical methods were available for veterinary pharmaceuticals. For this reason, the study included the development of new methods for several active ingredients. For all but a very few active

ingredients, no chemical analytical methods are available for the measurement of pharmaceuticals in suspended matter, sediment and manure.
In relation to the interpretation of the results, it should be noted that the chemical analytical methods require further development, in particular as regards quantification. Qualitative measurement (i.e. the identification of the substance) is reliable but the quantification of active ingredients of pharmaceuticals in surface and wastewater is not yet accurate enough for use in estimating risks to the environment. Reported concentrations of active ingredients in wastewater and surface water must therefore be regarded as only a rough indication of actual levels.

Wastewater

The survey showed that wastewater from a *residential area* contained household analgesics, lipid-lowering agents, beta-blockers and antiepileptics in concentrations of up to a few µg/l or tens of µg/l (reflecting their general use in the population). Antibiotics, x-ray contrast media and an anaesthetic were also identified, but in far lower concentrations.

Types and concentrations of pharmaceuticals identified in the wastewater from hospitals, pharmaceutical plants and fish farms varied widely from one source to another, reflecting the highly specific nature of the procurement/use of the pharmaceutical, the production processes and the discharge situations. *Hospital wastewater* featured high concentrations of x-ray contrast media and antibiotics other than those used in households. The highest concentrations of the x-ray contrast media in this type of effluent were around mg/l, while those of antibiotics amounted to a few µg/l or tens of µg/l.
In samples of wastewater from one *pharmaceutical plant*, concentrations of several antibiotics, analgesics, beta-blockers and an antiepileptic were comparable to or lower than those in municipal sewage. Concentrations of pharmaceuticals in the biologically treated effluent from another such plant were – with the exception of a single substance – below the detection limit. Concentrations of antibiotics found in wastewater from *fish farms* varied very widely from one farm or type of farm to another. In the effluent of those producing eel and trout for human consumption, no antibiotics could be detected. On one single occasion, malachite green was found. On the other hand, concentrations of antibiotics in wastewater from a wholesaler dealing in tropical fish, where the wastewater was being discharged directly to surface water without passing a treatment facility, was in the order of several tens of µg/l. This resulted in high concentrations of antibiotics in the receiving surface water downstream of the discharge point.

General municipal sewage and influents at sewage treatment plants (STPs) were very similar to sewage from a residential area, although containing higher concentrations of several specific antibiotics and x-ray contrast media. In addition, high concentrations of specific antibiotics were recorded from time to time at a number of locations, perhaps as a result of use in animal husbandry or tropical fish breeding. The removal efficiency of STPs for pharmaceuticals varied widely both from one group of substances to another and from one individual active ingredient to another within the same group. At present, removal rates for x-ray contrast media are very poor (< 10 %), followed by antibiotics (< 25 %) and antiepileptics, beta-blockers and lipid-lowering agents (10-80 %). By contrast, the rate for removal of household analgesics is over 95 %.

The report recommends further quantification of the (relative) contribution of the various sources of emissions to the pollution of surface water with human and veterinary pharmaceuticals. It suggests that attention should

focus on the potential sources of emissions of veterinary pharmaceuticals: intensive animal husbandry and fish farms.

Surface water

The substances most frequently identified in surface water (in at least 50 % of the locations) were: almost all x-ray contrast media, four analgesics, two antiepileptics (carbamazepine and primidone), two beta-blockers (sotalol and atenolol), two antibiotics (azitromycin and sulfamethoxazole) and one anaesthetic (lidocaine). Concentrations in surface water were significantly lower than those in wastewater, ranging from just a few nanograms to hundreds of nanograms per litre. Categories with concentrations exceeding 10 ng/l were: x-ray contrast media, analgesics, beta-blockers, antiepileptics and antibiotics. A number of individual pharmaceuticals were found in concentrations exceeding 100 ng/l: carbamazepine, diclofenac, ibuprofen, and the majority of x-ray contrast media.
Half of the over 100 active ingredients monitored never exceeded the detection limit. It is unclear whether these substances are in fact absent from the environment because of negligible or non-use in the Netherlands or whether the failure to detect them is due to sorption in sediment and suspended matter or fast transformations. Most of the data needed to clarify this point are (as yet) unavailable or are not in the public domain. It is also possible that active ingredients present in very low concentrations are escaping detection due to the relative crudity of current chemical analytical methods.

The incidence and concentrations of pharmaceuticals in Dutch wastewater and surface water did not prove to be significantly different from those reported in studies outside the Netherlands (primarily in Germany).

Risks to the environment

In terms of acute effects, pharmaceuticals may be expected to present virtually no risk to aquatic organisms. However, the problem is one of long-term exposure to low concentrations of a large number of pharmaceuticals designed to produce specific effects in organisms. Therefore, chronic and/or specific effects may be occur. These may include disturbance of the hormonal and immune systems or the development of resistance. Although very little is known about this, the information available suggests that risks cannot be ruled out.
As yet, virtually no methods are available to measure specific effects. In what tests are available (*in vitro* tests or biomarkers), the translation of the effect into impacts on the ecosystem is less simple than in the case of chronic tests. For this reason, tests of this kind tend to be used as screening tools, measuring exposure rather than effect.
The report suggests that, in order to identify the risks of pharmaceuticals in the environment, the first priority must be to focus on those substances expected to present the greatest risks. The selection of these substances should be based on a combination of high reported concentrations and available ecotoxicological information. On this basis, the top priority will be a small number of specific analgesics, antiepileptics, beta-blockers and lipid-lowering agents (because of their high concentrations in surface water), plus antidepressives and antineoplastic drugs (because of the serious environmental hazard they are expected to present to aquatic organisms). In addition, the report recommends that field samples should be tested with bioassays to assess the combined toxicity of the overall mixture of pharmaceuticals and hence the environmental risks.

To sum up, the study shows that human and veterinary pharmaceuticals are present in the Netherlands both in wastewater (whether or not biologically treated) and in surface water. Given the present paucity of relevant toxicity data, it is difficult to estimate the risks to aquatic organisms. In addition, it is still difficult to quantify many of the active ingredients from pharmaceuticals in environmental samples, even though qualitative analysis is now reliable. Nevertheless, taken together with the scanty ecotoxicological data, the concentrations found in the environment are sufficient to justify further research into sources of emissions, exposure pathways, presence in the aquatic environment and risks to aquatic organisms.