Executive Summary

Health Council of the Netherlands. Environmental risks of medicines. The Hague: Health Council of the Netherlands, 2001; publication no. 2001/17.

In recent years, medicines for humans and animals[a] have increasingly been found in the environment. Some medicines are known to disrupt the hormone system of fish, crustaceans and shellfish. Little more is known about some medicines than that they are found in low concentrations in water and soil. However, for the majority of medicines, practically nothing is known about their occurrence in the environment and the risks they present to organisms living in their natural habitat. In other countries, traces of medicines have been found in drinking water. However, no research has been conducted into the possible consequences of exposing human beings to the presumably low concentrations found in drinking water.

Medicines are detected in the environment at concentrations ranging from nanograms to micrograms per litre, a concentration range that is also characteristic for pesticide residues in the environment. Medicines are also biologically active substances that may have an undesirable impact at low concentrations. Therefore, after consulting specialists from within the Health Council, the Council's President concluded that it would be advisable to compile an overview of the available knowledge of medicines and their conversion products in the environment.

[a] 'Medicines' in this report refer both to medicines for humans and for animals unless specified otherwise.

Medicine use and their occurrence in the environment

Medicines for humans and animals are biologically active substances and are used in large volumes. During their production and use, a percentage of them enters the environment unchanged or as a metabolite. Medicines for humans generally enter the surface water through sewage treatment plants; they are usually inadequately removed in sewage treatment plants. Veterinary medicines enter the soil directly or indirectly from urine or manure. If they are not degraded or adsorbed, medicines that are reasonably or readily soluble in water are washed out and thereby transported to groundwater and surface water. Some medicines are readily degraded biologically or chemically, for example under the effect of light, whereas others have a persistent character.

Research into the occurrence of medicine residues in water and soil only started recently; very little is known about this aspect with regard to veterinary medicines in particular. It is true that the first measurements (clofibrin acid and nicotine) were made in the 1970s, but more extensive research into the occurrence of medicines in the environment has only been underway for approximately five years. This is being conducted in Germany, England, the United States and Switzerland, amongst other countries. It is still only concerned with a fraction of the substances classified as legally approved medicines. Measurements are primarily made in surface water, groundwater and drinking water, as well as in untreated sewage water (*influent*) and the treated sewage water (*effluent*) that flows into surface water from sewage treatment plants. Worldwide, until early in 2000, 83 medicines had been detected; they occurred in the concentration range from the detection limit in nanograms to micrograms per litre. Only in a few cases, traces were detectable in drinking water. Until now, attention has mainly been focused on hormones, antibiotics, cardiovascular medicines and painkillers.

On a number of dates in 1997, investigations in the Netherlands to detect the hormone 17α-ethinylestradriol (the active ingredient of the contraceptive pill) were conducted in the effluent of three urban sewage treatment plants and at eleven locations in the surface water. The hormone was found on two occasions in the effluent of one sewage treatment plant, at concentrations of 7.5 nanograms per litre. It was detected on four occasions in the surface water of the Rhine and Maas, at concentrations of up to 4.3 nanograms per litre. An exploratory study was conducted in the Netherlands in 1999 to determine the occurrence of eleven other medicines in the country's environment. Six medicines were detected in sewage treatment plant effluent (two sewage treatment plants sampled once); the highest measured concentration was 0.9 micrograms per litre; 5 medicines were detectable in the surface water (concentrations

up to 0.3 micrograms per litre). Drinking water was found to be unpolluted. It follows from data in international literature that extensive use of medicines leads to pollution, especially of surface water, groundwater, soil and occasionally drinking water (according to some measurements in Germany and the United Kingdom).

Impact

Little is known about the behaviour and impact and therefore the risk to plants and animals of medicine residues in the environment. The available information concerns around 10 percent of medicines and mainly applies to the water compartment. So far, studies have mainly focused on antibiotics, natural and synthetic hormones, antidepressants and substances used in chemotherapy for cancer. Even less is known about the behaviour and impact of metabolites.

Impacts on wild flora and fauna may be the result of the pharmacological effects of the medicine; they are expressed via receptors that are comparable with the target receptors in humans and domesticated animals. The effects may be similar or completely different. Antidepressants have numerous physiological effects on molluscs, crustaceans and insects, for example on the depositing of spawn by mussels or the release of certain neurohormones by crustaceans. It is also conceivable that the medicine affects receptors that only occur in wild flora or fauna.

Hardly anything is known about the impact of veterinary medicines in and on the soil; guesses mainly concern organisms that are exposed to relatively high concentrations. These include wild fauna in manure (micro-organisms, worms, flies and beetles) or animals that feed on these organisms (birds).

Regulations

Unlike with pesticides, the approval procedure for medicines for human use does not take into account environmental aspects, such as anticipated concentrations in soil and water or toxicity to plants and animals. Current regulations on the approval of medicines for human use therefore contain no provisions for assessing the environmental risks. Moreover, the regulations do not have provisions for any form of control after the medicines start to be used.

However, the approval procedure for veterinary medicines does require data to be provided about anticipated concentrations in the environment. According to the Veterinary Medicines Act, which is in line with European Directive 81/852/EEC, from 2003 data must be provided on the possible ecotoxicological risks of veterinary medicines, if an exposure threshold value is exceeded. The exposure threshold value is

not based on the veterinary medicine's toxicity; exposure below the exposure threshold value does not guarantee that there will be no impact.

Risks

The first step in assessing the risk of medicine residues in the environment should be to estimate the level of exposure. This requires at least data on the extent of use of individual medicines as well as data about the way the medicines are used or taken. By way of precaution, in the absence of data on conversion in patients, sewage treatment plants and the environment, it can be assumed that the medicine is not metabolized. (Taking this approach will generally result in an over-estimate of the concentration found in the environment). If the estimated exposure concentration is greater than an as yet unspecified exposure threshold value (the detection limit for example), a measurement of the actual concentration should be considered.

So far, investigations to detect the presence of medicines have mainly focused on water and to a lesser degree soil. The number of medicines investigated accounts for less than 10% of the total number in use. Now that chemical monitoring has increased in recent years, the number of medicines detected is growing. It is unclear how many medicines will eventually be detected. Estimates are inaccurate because information on the extent of use is not public. There is also a lack of information on the distribution, conversion and degradation of medicines. On the basis of current knowledge it is therefore impossible to say with reasonable certainty what the impact of medicines on the environment is. This does not permit the conclusion that there is no environmental problem. The information that is available gives cause for concern.

Concentrations of the same order of magnitude as those for pesticides are measured in surface water. The fact that medicines that are fairly readily broken down are nevertheless found in surface water is the result of the permanent supply from sewage treatment plants. Exposure of aquatic organisms to residues and metabolites of medicines therefore has a chronic character. The situation in the case of pesticides is different, as it is almost exclusively the persistent pesticide agents that have a long-term presence in the environment.

Information about the medicine's toxicity is required to estimate the environmental risk. In the absence of that information, the measured concentration of the medicine in an environmental compartment may serve as a *trigger* for a more detailed ecotoxicological study. The cardiovascular medicine metoprolol and the painkiller diclofenac, for example, have repeatedly been detected in surface water at concentrations in excess of a microgram per litre, yet the lack of ecotoxicity data makes a risk analysis impossible.

Because residues of medicines have been detected in drinking water in some cases, there is a question of whether this poses a risk to humans. Although this question cannot be answered definitively at the moment, the likelihood of an impact on humans appears to be small. This conclusion is based on the difference between the therapeutic dose used for humans and the concentration found in drinking water; the concentrations measured in drinking water are one millionth or less of the concentration for which a therapeutic effect occurs.

Conclusion

As up to now research and monitoring efforts are limited to about 10% of the medicines in use, it is likely that many more medicines than known at present occur in the environment. The measured concentrations are rather low, but one should keep in mind that medicines are biologically active substances. Given the continuous supply of fresh residues, organisms in the environment are exposed chronically. As the present report demonstrates, very little is known about ecological risks of medicine residues. The data that are available, suggest that such risks are not *a priori* to be classified as insignificant.

The conclusion of the present report is that the government would be justified in paying extra attention to the risks posed to the environment by medicine residues. That would be consistent with the attention paid to pesticides. The research and monitoring efforts should focus on the nature and extent of the exposure and the chronic effects on organisms in water and soil.

Research recommendations

Development of specific tests

Research into the possible environmental impact of medicines can be based on experiences with pesticides. Research is necessary into acute and chronic toxicity to enable an assessment of the permissibility of a pesticide. The end points for a pesticide assessment are often non-specific - for example mortality, growth, and reproduction - or are concerned with the pesticide's known effect – such as inhibition of algal growth in the case of a herbicide. However, the effects of medicines and pesticides arise from different mechanisms. This means that for some medicines the standard set of test instruments will be inadequate.

The aforementioned difference in the way in which medicines have an impact on the environment is also important. In the case of medicines, it would be advisable to

develop additional tests that correspond with the concentrations that are actually detected in surface water, soil and manure, and for the end points of the tests to correspond with the wide spectrum of pharmacological effects. For example, in the case of substances with a genotoxic, antibiotic, hormonal or immunological effect, additional tests should be developed that take into account that effect. When developing adequate tests, it is also necessary to take into account the medicine's side effects. The duration of the test should also correspond with residence time in the environment and the time necessary for the effect to be expressed. In the case of additional tests for medicines, attention could be paid to chronic tests for aquatic organisms and acute and chronic tests for soil organisms. It is currently impossible to say which plant and animal species are representative in ecotoxicological research and which end points ought to be studied.

Practically nothing is known about the concentrations of metabolites of medicines in the environment and about their environmental toxicity.

Increased monitoring

More extensive *chemical* monitoring makes a more accurate estimate of the extent of environmental pollution possible. The results of the monitoring survey are also essential for improving and validating models used for estimating concentrations in the environment.

The minimum requirement in terms of the choice of medicines to be analysed is access to details of the extent of use. Information on toxicity to plants and animals is also necessary for making an efficient selection of medicines that have to be sought. This will require considerable research effort that pays particular attention to the choice of relevant end points. In the absence of ecotoxicity data, detailed information from pharmacological and toxicological research in connection with the development of medicines may provide an insight into the vulnerability of other organisms. This information would have to be provided by medicine producers.

Monitoring effects in surface water and soil appears to have little chance of success because the expectation is that the effect will often be unobservable (or will be difficult to link to a medicine residue). This will play a particular role in the case of unknown chronic mechanisms of effect, which will be seen in the ecosystem as a subtle effect on ecological relationships. In the case of a specific effect, as in the case of research into the disruption of the sex hormone system in aquatic organisms, field research could have an indicative function.

Modification of water treatment technology

An investigation of process technology should be carried out to determine whether sewage treatment could be improved to break down medicine residues more effectively than in existing sewage treatment plants.

International co-ordination

The extent of the recommended research warrants a co-ordinated and, if possible, international approach. This could include the development of test strategies for ecotoxicity, the development and validation of distribution models, method development for risk assessment and setting requirements for information on the use of medicines.

An international co-ordinated approach already exists for the approval assessment made by the *Veterinary International Committee for Harmonisation* (VICH). In this regard, active involvement by the Dutch government in the environmental assessment of veterinary medicines and human medicines would be advisable, for example through the *Committee for Veterinary Medical Products* (CVMP).