

# Pharmaceuticals – Permanent Pollutants in Environment

## Basic facts and proposed measures to protect the public health and the environment

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## SUMMARY

Pharmaceuticals used in humans and for the production of food pose an environmental problem that is still not properly recognized. Although the research has developed during the last decade, much more research is needed.

Pharmaceuticals comprise one of few groups of chemicals specifically designed to act on living cells. Pharmaceuticals are excreted, intact or metabolized, mainly into the urine. They are degraded to various extents in the sewage treatment plants, but some of them leave the plant in active form.

In the recipient water, the pharmaceutical residues may have effects on living organisms. Observed effects in fish include intersex changes, impaired reproductive potential, and tissue accumulation of active substances. In developed countries there is an almost ubiquitous appearance of drug residues in surface and ground water. Low concentrations of pharmaceuticals are also regularly observed in drinking water.

To protect water sources from pollution, producers should attempt to design future pharmaceuticals to be eliminated before leaving the sewage treatment plant. Legal requirements and conscientious prescription of medicine may stimulate the producers to do so. The use of pharmaceuticals should be reduced by exploiting the full potential of non-pharmacological treatments.

Nevertheless some pollution is inevitable and therefore sewage and water treatment plants must be upgraded technically to meet the problem with currently existing emissions of stable pharmaceutical residues.

Unless proper measures are taken, long-term emissions of pharmaceuticals into the environment may yield impaired public health, particularly developmental disturbances in children, and severe ecological disturbances.

**As doctors, we must demand that pharmaceuticals are recognized as chemicals, with negative effects on environment, and possible indirect negative effects on human health. Pharmaceuticals should be managed as organic and persistent pollutants.**

## MANUFACTURE OF PHARMACEUTICALS

Pharmaceuticals are manufactured from plants, fossil oil, coal and minerals. Their packaging uses fossil oil, minerals and wood. To produce energy for production and transport, nuclear power, fossil fuels and hydropower are used.

Residues are the visible and invisible waste products (diffusely dispersed), which arise from the exploitation of raw materials in production, transport and consumption/use of drugs and drug packages.

The manufacture of the active substance often occurs in countries other than where the pills or solutions are produced and consumed. Some factories release large quantities of active substances, including broad spectrum antibiotics. The waste water from pharmaceutical industries is sometimes highly toxic.

## ENTRY OF PHARMACEUTICALS INTO THE ENVIRONMENT

Residues of pharmaceuticals used by humans are usually excreted into their urine and/or faeces. Since most urban households and hospitals are connected to a public sewage system such residues may usually go to a public sewage treatment plant (STP). Dermally applied pharmaceuticals are also delivered to STP's. In the countryside, household and private sewage treatment systems are often less efficient.

Pharmaceuticals from treated animals in most cases reach the terrestrial environment following excretion. Thus, pharmaceutical residues excreted via urine or faeces from treated humans or animals may reach the public STP's, private treatment plants, surface water or soil, depending on prevailing conditions. There are no data to assess the relative importance of the emission load of pharmaceutical residues to these various sites. Emission into the atmosphere via expiration from treated humans or animals is probably of less importance in this context.

Disposal of unused or expired medicinal waste from hospitals or households offers a significant source of pharmaceutical contamination of the environment. Earlier the possible negative impact of such disposal was not recognized. It was recommended by producers and pharmacies that unused or expired medicines should be flushed down the toilet (such recommendations still appear in many countries). Medicines flushed down the toilet will, of course, reach the sewage system and hence be subject to the same processes as those excreted from treated patients.

Medicines disposed with other household waste will reach the garbage dump. If the garbage is incinerated, the degree of destruction of organic synthetic molecules, including pharmaceuticals, is dependent on the incineration temperature. The possible environmental impact of pharmaceutical residues following incineration is consequently dependent on local conditions, including treatment and handling of residual ashes. If, on the other hand, household garbage is deposited openly, leakage of chemicals, including pharmaceutical residues, will eventually take place into the ground water.

If the sewage water from chemical plants is not treated appropriately, residues of pharmaceuticals may be ingested by individuals. This is probably less common in high income countries than in low income countries such as China and India, where control is more likely to be inadequate, and where a large proportion of the active substances are manufactured.

## OCCURRENCE AND ENVIRONMENTAL EFFECTS OF PHARMACEUTICALS

The excretion of pharmaceuticals used by humans is mainly directed towards the aquatic environment. The effluents from STP's contain pharmaceuticals in the low µg per litre range, yielding surface water concentrations in the low nanograms (ng) per litre range after effluent dilution. Observations on surface water concentrations have been reported from the US, Germany, Sweden, and other countries.

Concentrations in surface water alone are not sufficient to assess the risk of negative environmental effects in the aquatic environment. Thus, estrogenic compounds like ethinyl-estradiol at concentrations < 1 ng per litre may cause both vitellogenin production (a frequently used index for feminization of male fish), and structural change in their sex organs. It has also been demonstrated that fish exposed to STP effluent can take up and concentrate estrogenic compounds, including ethinyl-estradiol, to very high internal levels. These observations on feminization of fish by estrogenic compounds in STP effluents have been observed in many countries, and have also been observed in other species, like frogs, alligators and molluscs.

Other examples of environmental impact in the aquatic environment of human medication concern both cardiovascular and neuro-psychiatric medicines. The non-selective beta-blocking agent propranolol was found to cause a significant decrease in egg production in medaka fish, at a concentration close to that demonstrated in

STP effluents. Gemfibrozil, a fibrate frequently used to lower blood fat levels in patients with hyperlipidemia, often appears in the effluent from STPs. At concentrations close to those reported in STP effluent, gemfibrozil lowers the blood levels of testosterone in fish.

Some selective serotonin reuptake inhibitor anti depressants (SSRI's) have been shown to accumulate in exposed fish. Citalopram has been detected in liver from wild perch in low  $\mu\text{g}$  per kg levels, and fluoxetine affects the serotonin system in the same way that it does in humans. Fluoxetine has also been shown to affect swimming activity in shellfish; whether this is linked to a disturbance of serotonin function in the brain is unknown.

The presence of antibiotics in sewage plants composes a special problem. This might reduce the bacterial clearing of other toxins, cause ecologic effects on microbes downstream, and increase the risk of the emergence of resistant bacteria.

## DEVELOPMENT OF RESISTANT BACTERIA AND VIRUSES

High levels of antibiotics in the water are a cause for alarm as there is an increased risk of selecting resistant bacteria, an issue of global concern. This can lead to some highly effective antibiotics that are becoming ineffective.

The term "eco-shadow" has been introduced to describe the ecological impact of antibiotics. Antibiotics with a wide spectrum that are also stable will have a greater impact on the bacterial flora (a long eco-shadow) than those with a narrow antibacterial spectrum which disintegrates more rapidly (a short eco-shadow).

The ecological effects of tetracyclines and quinolones have been observed. They are not metabolized in the human body and are therefore excreted unmodified. They are poorly degraded in nature. They can be toxic to other animals, particularly fish. In the effluent from a sewage plant in India, several broad spectrum antibiotics were found in concentrations toxic to bacteria and plants. In the sewage plant itself, there were enterococcae resistant to all known antibiotics.

The development of resistant bacteria in sewage plants is stimulated by high concentration of antibiotics (e.g. in plant sewage), large amounts of bacteria (e.g. from human sewage water that is added in plant sewage), and selection of bacteria via active slime technology (bacteria are chosen that can resist the antibiotics).

Oseltamir does not break down in sewage plants. The active substance has been found in water where birds with influenza virus were living thus raising the possibility that resistance might occur.

## PHARMACEUTICALS IN SURFACE WATER AND PUBLIC HEALTH

The levels of pharmaceuticals in surface or drinking water are generally below 100 ng per litre. This low concentration might appear to guarantee that they hardly pose any problem to public health. Assuming a concentration of 100 ng/l of a pharmaceutical that in humans has DDD (defined daily dose<sup>1</sup>) of 10 mg implies that a volume of 100,000 liter would be required to make up one single DDD. Such calculation, however, is an over-simplification that does not take into account several important dynamic aspects of the low concentrations of pharmaceuticals in the water.

Firstly, aquatic organisms may accumulate lipid soluble chemicals, including pharmaceuticals. It is well known that certain fish species, like herring, may contain very high concentrations of the persistent and lipophilic chemicals DDT (dichlorodiphenyl-trichloroethane, an insecticide) and PCB (polychlorinated bisphenols, a group of industry chemicals earlier used in e.g. building materials).

Secondly, pharmaceuticals and other anthropogenic chemicals enter the aquatic environment to form a cocktail, with hundreds or even thousands of ingredients. Even if exposure to a single component in this cocktail may be considered harmless from a toxicological point of view, there are currently no methods to assess the overall effect of this exposure.

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<sup>1</sup> WHO definition: The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

Thirdly, when a new medicine is developed, its pharmacological and toxicological effects are tested in acute trials, before being accepted for marketing. However, clinical test procedures are not entirely sufficient to completely guarantee that a new pharmaceutical is devoid of unacceptable side effects when used in large cohorts of patients for a long time. Furthermore, there are currently no test methods to assess whether such effects may occur after long-term use in humans.

## OVERUSE OF PHARMACEUTICALS

Pharmaceuticals are considered to be the most important tool for doctors today. One of the reasons has been that there is no scientific evidence for non-pharmaceutical methods. However, today the evidence is growing that non-pharmaceutical methods might substitute or reduce the needs of pharmaceuticals. The evidence for the danger of pharmaceuticals is also growing, as new reports on side effects are published. To exchange the pills of modern medicine, where side effects and to some extent environmental effects are documented, for pills of traditional or complementary medicine, where we have very little knowledge, is not the right solution.

There is a need to include a wider range of treatments in the ordinary health care. Examples are smoking cessation before elective surgery, music during anesthesia, rehabilitation in nature and cognitive therapy in depression.

The prescription method can be used, both as prevention and as part of the treatment. Some of the non-medical treatments that could be prescribed are

- Stop or never start smoking;
- More physical activity;
- Reduced alcohol consumption;
- More vegetables, fruits, nuts, fish; less “junk food”, red meat, sweet drinks;
- Stress reduction and mental strengthening;
- Better sleeping quality;
- Safe sex habits;
- Less use of illegal and legal drugs.

The public and patients must be educated to accept these treatments. The society must be planned to promote a healthy lifestyle. Research on non-pharmaceutical treatments should be encouraged.

## THE EUROPEAN UNION DIRECTIVE

In the European Union, the new directive for human pharmaceuticals explicitly requires that all member states should establish collection systems for unused or expired medicines. Such systems were already in use in several member countries at the time the new legislation went into action in 2004. Nevertheless, the extent to which such systems have been established and made publicly known, varies between regions. Furthermore, the directive does not regulate how the collected pharmaceuticals should be handled. Disposal into the sewage system is still a legally accepted route of elimination. However, incineration at high temperature (1200 degrees centigrade) is a preferred alternative to avoid environmental pollution.

At present, although quantitative data are not available, it can be assumed that a large portion of excreted or disposed medicines reach the public STP's. Alternatively, the sewage is directly let out into various surface waters like rivers, lakes, streams or the open sea.

## LEGAL REQUIREMENTS

Pharmaceuticals differ from other anthropogenic chemicals with respect to legal requirements. They are regularly excluded in laws and regulations which control manufacture, marketing, use, and disposal of other consumer products of a chemical character (solvents, paints, glues etc). As a consequence the possible negative environmental impact of pharmaceuticals is much less documented, in comparison to other consumer chemicals. For pharmaceuticals approved for marketing before 1995, there are no requirements for documentation of environmental effects. Hence, pharmaceuticals which have been on the market for decades may have serious environmental effects that have not been detected.

## POSSIBLE PROTECTIVE MEASURES

The European Commission has, in its new directive for human as well as for veterinary medicinal products, introduced several paragraphs dealing with environmental issues. Most important is the requirement for an environmental risk assessment connected to the application for marketing of a new pharmaceutical substance, and the legal claim for protective measures to diminish the environmental risk in specific cases. In addition, all member countries are required to develop collection systems for unused or expired medicines (cf. above). In the directive for human medicines, marketing approval can be refused if the product deemed to be a threat to public health and in the veterinary directive refusal for marketing can be based on negative environmental properties in general. The new directives went into action in 2004, and the guiding document on environmental risk assessment of pharmaceuticals was launched by the European Medicines Agency (EMA) in 2006.

Measures to protect the aquatic environment from pharmaceutical pollution have also been taken. In Sweden, pharmaceutical producers and health care providers have jointly developed a system for environmental classification of risks and hazards of all human pharmaceutical substances. The idea is to provide an instrument for doctors and patients to choose the environmentally most favourable alternative when two or more medically equivalent pharmaceuticals are available in a specific condition. It is assumed that the user's access to environmental classification will induce a shift in market preference towards environmentally better choices, and that such a market shift will stimulate producers to develop future pharmaceuticals to be more environmentally acceptable. The classification system has gained interest in several EC member countries, including Germany, the Netherlands and Denmark.

There is also a growing interest in the US on the possible environmental effects of pharmaceuticals. Some hospital chains have very ambitious environmental protection programs, and systems for safe collection of expired or unused medicines are being established on a voluntary basis.

## WHAT SHOULD BE DONE AT WHO AND UNEP LEVEL?

- Official and community recognition of pharmaceuticals as chemicals, with negative effects on environment, and possible indirect negative effects on human health.
- Inclusion of pharmaceuticals among organic and persistent pollutant;
- Inclusion of Pharmaceuticals and Environment as a topic at the next conference on chemical safety.

## WHAT SHOULD BE DONE AT EU LEVEL?

- Standardise risk definition for human and veterinary medicines, i.e. include risks to the environment in the risk-benefit assessment for human medicinal products.
- Request that the Commission develop an environmental classification of pharmaceuticals for the EU, based on their risks and hazards, and to consider how the information yielded should be made available to prescribers, pharmacists, and patients.
- Request that the Commission consider the inclusion of pharmaceuticals in other EU directives, and decide on regulations, rules and acceptable levels for pharmaceuticals in surface and drinking water.
- Assess the possibility of reducing emissions into the environment from production sites as part of Good Manufacturing Practice (GMP).
- Assess the possibility to accept prolonged durability of pharmaceuticals ahead of the current 2 or years.

## WHAT SHOULD NATIONAL MEDICAL ASSOCIATIONS DO?

- Recognize that the medical profession has some responsibility for pharmaceuticals in the environment and propose a motion to WMA to adopt the issue.
- Encourage use of non-pharmaceutical treatments, instead of or complementary to pharmaceutical treatments, and demand that governments, insurance companies and other financing bodies give economic support for this.
- Support and demand research on non-pharmaceutical treatments as well as research on environmental friendly pharmaceuticals.

## WHAT SHOULD INDIVIDUAL DOCTORS DO?

As doctors, we have several options to reduce the environmental effects of pharmaceuticals:

- Try lifestyle changes before prescribing pharmaceuticals;
- Only prescribe pharmaceuticals that one is sure the patient will take;
- Be restrictive with prescribing if one is not sure of the benefit to the individual patient;
- Prescribe only small amounts of new medicines;
- Regularly reconsider long term ordinations;
- Avoid prescribing pharmaceuticals with long life in the environment when alternatives exist;
- Use the Swedish classification system for more environmentally friendly prescriptions;
- Avoid prescribing pharmaceuticals where only a small amount of the active substance is used, e.g. plasters;
- Ask every representative from the pharmaceutical companies about the preparation's effects on the environment – firstly the degradation speed, and secondly the circumstances under which the active substance has been manufactured;
- Remind patients and relatives that unused medicines should be taken care of in a safe way.

## FURTHER READING

Links to these and other references are found at Swedish Doctors for the Environment [www.lakareformiljon.se](http://www.lakareformiljon.se).

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