Pharmaceuticals in the environment – the global perspective
Occurrence, effects, and potential cooperative action under SAICM
Pharmaceuticals in the Environment

Summary

Pharmaceuticals are a crucial element of modern medicine and confer significant benefits to society. About 4,000 active pharmaceutical ingredients are being administered worldwide in prescription medicines, over-the-counter therapeutic drugs, and veterinary drugs. Their active ingredients comprise a variety of synthetic chemicals produced by pharmaceutical companies in both the industrialized and the developing world at a rate of 100,000 tons per year. While pharmaceuticals are stringently regulated for efficacy and patient safety, the adverse side effects they may have in the natural environment have not yet been sufficiently studied and are not covered by an international agreement or arrangement.

Pharmaceutical residues have been increasingly measured in the environment over the past decade, mostly in surface waters, but also in groundwater, soil, manure, biota, and even in drinking water. Since pharmaceuticals are specifically designed to cause pharmacological effects in living organisms, it is not surprising that a growing body of literature has shown that pharmaceuticals are having adverse effects on wildlife and ecosystem health. It is challenging to assess the potential long-term health risks of trace amounts of pharmaceuticals in drinking water, especially given that drinking water is currently not systematically monitored for pharmaceutical residues. This situation has triggered public concerns about the aesthetic-hygienic quality of drinking water.

With better access to health care in developing nations and aging populations in industrialized countries, the production, use, and disposal of pharmaceuticals is expected to grow. As a result, unless adequate measures are taken to manage the related risks, pharmaceuticals will increasingly be released into the environment.

Nomination as an emerging policy issue under SAICM

The Strategic Approach to International Chemicals Management (SAICM) has identified “Environmentally Persistent Pharmaceutical Pollutants” (EPPP) as a possible emerging policy issue for the International Conference on Chemicals Management (ICCM) to consider at its fourth session. An extended nomination dossier (SAICM/OEWG.2/INF/15) has been developed by the Ministry of Environment of Peru, the Ministry of Housing, Land Planning and Environment of Uruguay and the International Society of Doctors for the Environment for consideration at the second meeting of the Open-ended Working Group (OEWG2), to be held in Geneva on December 15-17, 2014.

A workshop held in Geneva on April 8-9, 2014 (www.pharmaceuticals-in-the-environment.org) concluded that SAICM could be used as a voluntary policy framework to address the issue of pharmaceuticals in the environment on a global scale. This could be done without compromising the effectiveness, availability, or affordability of medical treatment, especially in countries in which access to health care is still limited. Cooperative action under SAICM could initiate a multi-sectoral, multi-stakeholder, life-cycle approach to preventing, reducing, and managing pharmaceuticals in the environment.
1. Emission pathways of pharmaceuticals entering the environment

After passing through the body, pharmaceutically active ingredients are excreted either in an unchanged active form or as a metabolized substance (Figure 1). Municipal sewage collects a variety of human pharmaceuticals (and their metabolites) administered in households, hospitals, and for elderly care. Unused medicines that are improperly disposed in sinks and toilets also end up in municipal sewage. Conventional sewage treatment facilities, including activated sludge processes, do not fully remove pharmaceuticals from wastewater; indeed, removal efficiencies range from less than 20% to more than 80% for individual pharmaceuticals. Thus, residues are released into rivers, lakes, and groundwater aquifers. In addition, pharmaceutical manufacturing facilities have been shown to release active ingredients into nearby streams (Larsson et al. 2007).

Veterinary pharmaceuticals applied in animal husbandry are released into the soil environment where manure is used as fertilizer. Over time, residues from these drugs accumulate in the soil or drain into groundwater or surface water; they may also be taken up by plants (Carter et al. 2014). Veterinary pharmaceuticals used in aquaculture directly enter surface waters.

In the environment, transformation and degradation reactions alter the mobility, persistence, and fate of the pharmaceutical residues.

Figure 1: Main emission pathways of human and veterinary pharmaceuticals entering the environment.
2. Monitoring pharmaceutical residues in the environment

Advanced methods are required to monitor pharmaceuticals in different environmental matrices (e.g., surface water, groundwater, soil) at the relevant concentrations, in some cases down to nanograms per litre. The required instrumental equipment – such as gas chromatography or liquid chromatography coupled to tandem mass spectrometry (GC-MS/MS or LC-MS/MS) – is quite expensive, both to acquire and maintain. While reliable methods have been established at laboratories worldwide, there is currently no internationally standardized analytical protocol for pharmaceuticals. Such a protocol could help to ensure both the quality and comparability of data.

3. Global occurrence in the environment

A growing body of literature demonstrates that pharmaceutical residuals are found globally in the environment (IWW 2014; Hughes et al. 2013). Based on a review of more than 1,000 international publications, pharmaceutical residues have been detected in 71 countries worldwide in all five UN regional groups (Figure 3). Pharmaceuticals have mostly been detected in surface water and sewage effluent, but they have also been found in groundwater, manure, soil, and other environmental matrices. More than 600 active pharmaceutical substances (or their metabolites and transformation products) have been detected in the environment. These belong to a variety of therapeutic groups:

- antibiotics,
- analgesics,
- lipid-lowering drugs,
- beta-blockers,
- x-ray contrast media, and
- synthetic estrogens.

While most findings have been published in industrialized countries, monitoring campaigns are increasingly being conducted in developing and emerging countries; these have revealed the global scale of the occurrence of pharmaceuticals in the environment. For example, diclofenac, a non-steroidal inflammatory drug, has been detected in the aquatic environment in 50 countries worldwide (Figure 4). A number of globally marketed pharmaceuticals have been found in both developing and industrialized countries (Table 1). Regional differences in medicinal consumption patterns, access to health care, and sewage treatment help to explain the variation across countries.
In rivers and lakes that receive wastewater, pharmaceuticals are often found in concentrations of 0.1 µg/L to 1.0 µg/L. However, maximum concentrations in densely populated areas or downstream of sewage treatment plants may be considerably higher. Less data is available on pharmaceuticals in manure and soil, but residues have been detected in 28 countries, especially in the vicinity of intense animal husbandry.

Table 1: Several globally marketed pharmaceuticals have been found in the aquatic environment of all UN regional groups (IWW 2014).

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Therapy Group</th>
<th>Number of countries worldwide in which pharmaceuticals have been found in the aquatic environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Analgesics</td>
<td>50</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Antiepileptic drugs</td>
<td>48</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Analgesics</td>
<td>47</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Antibiotics</td>
<td>47</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Analgesics</td>
<td>45</td>
</tr>
<tr>
<td>Estrone</td>
<td>Estrogens</td>
<td>35</td>
</tr>
<tr>
<td>17-β-Estradiol</td>
<td>Estrogens</td>
<td>34</td>
</tr>
<tr>
<td>17-α-Ethinylestradiol</td>
<td>Estrogens</td>
<td>31</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Antibiotics</td>
<td>29</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Analgesics</td>
<td>29</td>
</tr>
<tr>
<td>Clofibric acid</td>
<td>Lipid-lowering drugs</td>
<td>23</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Antibiotics</td>
<td>20</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Antibiotics</td>
<td>16</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Estrogens</td>
<td>15</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Antibiotics</td>
<td>15</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Analgesics</td>
<td>15</td>
</tr>
</tbody>
</table>

Figure 3: Global occurrence of pharmaceuticals: Pharmaceuticals have been found in the environment in all UN regional groups (IWW 2014).
4. Effects in the environment

Pharmaceuticals are biologically active substances that specifically affect control mechanisms in living organisms, for example by regulating metabolism, influencing hormonal balance, or alleviating signal transmission between cells. When released into the environment, this biological activity may adversely affect wildlife (so-called non-target organisms) and impair ecosystem health. This can occur through a variety of mechanisms, some of which have been demonstrated in laboratory and field observations (Table 2); others may yet be discovered.

Prominent examples of demonstrated ecotoxicological effects include (1) a near-extinction of vultures on the Indian subcontinent, which was caused by the birds’ feeding on the carcasses of cattle treated with the anti-inflammatory drug diclofenac; (2) a lake experiment involving the synthetic estrogen ethinylestradiol, which is used in birth control pills, that resulted in feminized male fish; and (3) effects of veterinary use of the parasiticide ivermectin on dung decay, dung insect populations, and aquatic invertebrates.

To assess the environmental risks, predicted (or measured) concentrations of pharmaceuticals in the environment are compared with Predicted No-Effect Concentrations (PNEC), which are derived from standardized laboratory experiments with model organisms such as algae, daphnia, fish, or plants. In the European Union, an environmental risk assessment is mandatory for newly marketed drugs (EC 2001a, b), but most commonly used drugs were introduced before the regulation came into force and thus have not been assessed.

The anti-inflammatory drug diclofenac provides a telling example. Maximum concentrations of the drug in surface waters have been measured above PNEC levels in 34 countries (Figure 4). This suggests adverse ecotoxicological effects on organisms at these locations. The highest concentrations often occur downstream of sewage treatment plants in densely populated areas.

![Diclofenac in surface waters: Highest concentrations measured](image)

Figure 4: Highest diclofenac concentration in surface waters reported in comparison to the Predicted No-Effect Concentration (PNEC) of 0.1 µg/L.
Antibiotic resistance

An alarming public health threat is the spread of pathogenic organisms that are resistant to antimicrobials. The presence of antimicrobials in the gut of humans and treated animals leads to the development of resistant bacteria and genes that can be excreted in faeces and spread to wastewater, sludge, manure, or soil. However, resistance genes can also develop in the environment if antibiotic residues are present; these genes can then be transferred to pathogenic bacteria (Allen et al. 2013). There is also evidence of an exchange of resistance genes between environmental bacteria and clinical isolates (Forsberg et al. 2012). Thus, strategies to reduce the introduction of antibiotics into the environment can also help to contain antimicrobial resistance (WHO 2014).

Endocrine-disrupting pharmaceuticals

Some pharmaceuticals have an endocrine function, which means they affect the hormone system. Examples of these include contraceptives, some cancer treatments, medicines for thyroid and nervous system diseases, and several veterinary drugs. Some endocrine-disrupting pharmaceuticals have been found to have adverse effects on wildlife at very low concentrations, such as feminizing male fish, preventing reproduction, or triggering population collapse (Kidd et al. 2007). These pharmaceuticals are a subgroup of endocrine-disrupting chemicals (EDC), which the SAICM has addressed as an emerging policy issue since 2012 (UNEP & WHO 2013).

Table 2: Some selected examples of adverse effects of pharmaceuticals on non-target organisms in laboratory, field, and environmental observations.

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Therapeutic group</th>
<th>Non-target organism</th>
<th>Effects</th>
<th>Study type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Analgesics</td>
<td>Vulture (Gyps bengalensis)</td>
<td>Population collapse due to renal failure</td>
<td>Wildlife</td>
<td>Oakes et al. 2004</td>
</tr>
<tr>
<td>17β-Ethynylestradiol</td>
<td>Synthetic estrogen</td>
<td>Fathead minnow (Pimephales promelas)</td>
<td>Population collapse due to feminization of male fish</td>
<td>Whole-lake experiment</td>
<td>Kidd et al. 2007</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Analgesics</td>
<td>Rainbow trout (Oncorhynchus mykiss)</td>
<td>Strong reactions of liver, kidney, and gills</td>
<td>Laboratory</td>
<td>Tisebukom et al. 2007</td>
</tr>
<tr>
<td>Flutamide</td>
<td>Antibiotics</td>
<td>Dung fly and beetle</td>
<td>Death of maize at high conc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Analgesics</td>
<td>European perch (Perca fluviatilis)</td>
<td>Altered behaviour and feeding rate</td>
<td>Laboratory</td>
<td>Foster et al. 2010</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Veterinary parasiticide</td>
<td>Dung fly and beetle</td>
<td>Mortality of eggs and larvae</td>
<td>Laboratory and field</td>
<td>Liebig et al. 2010</td>
</tr>
<tr>
<td>Enrofloxacin, Ciprofloxacin</td>
<td>Antibiotics</td>
<td>Cyanobacterium (Anabaena flosaquae) Duckweed (Lemna minor)</td>
<td>Growth inhibition</td>
<td>Laboratory</td>
<td>Ebert et al. 2011</td>
</tr>
</tbody>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Oxazepam</td>
<td>Anxiolytics</td>
<td>European perch (Perca fluviatilis)</td>
<td>Altered behaviour and feeding rate</td>
<td>Laboratory</td>
<td>Brodin et al. 2013</td>
</tr>
<tr>
<td>17β-Ethynylestradiol</td>
<td>Synthetic estrogen</td>
<td>Frog (Rana pipiens)</td>
<td>Mortality of eggs and larvae</td>
<td>Laboratory</td>
<td>Liebig et al. 2010</td>
</tr>
<tr>
<td>Azadirachtin</td>
<td>Insecticides</td>
<td>Nile tilapia (Oreochromis niloticus)</td>
<td>Growth inhibition</td>
<td>Laboratory</td>
<td>Ebert et al. 2011</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Analgesics</td>
<td>Coke block beetle</td>
<td>Death of maize at high conc</td>
<td>Greenhouse</td>
<td>Michalini et al. 2012</td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Veterinary parasiticide</td>
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Table 2: Some selected examples of adverse effects of pharmaceuticals on non-target organisms in laboratory, field, and environmental observations.
Pharmaceuticals have also been found in drinking water, largely at concentrations several orders of magnitude below the minimum therapeutic doses. The substantial margins of safety for individual substances suggest that appreciable adverse impacts on human health are very unlikely at current levels of exposure in drinking water (WHO 2012). However, at the local level, the production of pharmaceuticals has led to relatively high concentrations in well water that is used as drinking water (Fick et al. 2009). Systematic monitoring programmes are scarce, and there have been few comprehensive, systematic studies of the occurrence of pharmaceuticals in drinking water. This lack of data presents a key challenge to assessing the potential health risks of long-term, low-level exposure to pharmaceuticals in drinking water, especially for vulnerable sub-populations, including infants and the chronically ill.

In addition, if pharmaceuticals are repeatedly detected in drinking water – even at concentrations below what is considered harmful – the public may lose confidence in the overall quality of their drinking water. The precautionary principle calls for actions to minimize the occurrence of pharmaceuticals in drinking water.

**6. Potential cooperative action**

Cooperative action under SAICM could initiate a multi-sectoral, multi-stakeholder approach to prevent, reduce, and manage pharmaceuticals entering the environment on a global scale. Such action can be taken without compromising the effectiveness, availability, or affordability of medical treatment. To follow through on such an approach, the following stakeholders might need to be involved in taking coordinated, cooperative action:

- Intergovernmental organizations
- National governments, regulatory agencies and authorities
- Pharmaceutical companies, both innovative and generic
- Health care professionals, i.e. medical doctors, hospitals, and pharmacists
- Patients
- Veterinarians, farmers, and aquaculture operators
- Municipal sewage treatment plant operators
- Development cooperation
- NGOs
- Health insurance institutions
- Drinking water utilities
- Academia
In what follows, selected examples of work areas and associated activities are proposed for further discussion, each of which could help to reduce the occurrence and effects of pharmaceuticals in the environment. Suitable work areas may differ between countries and appropriate activities should be selected based on regional conditions. The work areas and activities are structured according to the five categories of objectives of the overarching policy issues under SAICM.

A. Risk reduction

- **Prioritizing action**
  Develop a work plan that builds on existing national and international activities.

- **Monitoring campaigns**
  Conduct monitoring campaigns to identify affected watersheds to support decision-making process, prioritization of actions, guidance and training tools involving relevant expertise.

- **Cleaner production**
  Promote the transfer and adoption of cleaner production technologies and pollution prevention policies, in particular best available techniques and best environmental practices (BAT/BEP). Extent Good Manufacturing Practice (GMP) to incorporate environmental quality guidelines.

- **Green procurement**
  Strengthen green procurement in health-care sector, e.g., building on the Joint UN Programme of Green Procurement in the Health Sector.

- **Veterinary medicine**
  Promote measures to reduce metaphylactic subscription in animal husbandry and aquaculture, including promotion of non-chemical alternatives.

- **Disposal of unused/expired pharmaceuticals**
  Establish and promote Best Management Practices for collection and disposal schemes, e.g., drug take-back programmes.
  Establish adequate facilities for management of pharmaceutical waste (e.g., incineration facilities).

- **Improve sanitation and sewage treatment**
  Promote access to sewage connection and biological sewage treatment for sanitation and hygienic reasons, which – as a secondary effect – would help to reduce the amount of pharmaceuticals entering the aquatic environment.
B. Strengthening knowledge and information

- **Global awareness raising**
  Raise global awareness about the adverse effects of pharmaceuticals entering the environment, with the aim of affecting patterns of prescription, usage, and disposal (e.g., discouraging people from flushing unused drugs down the toilet).

- **Scientific advice**
  Provide up-to-date information and support to decision makers, e.g., by creating an international network of scientists and risk managers to facilitate information exchange, and by requesting the International Programme on Chemical Safety (IPCS) to produce a state-of-science report.

- **Classification and labelling scheme**
  Provide information on environmentally benign pharmaceuticals to guide procurement, prescription, purchase, and usage behaviour, in cases where alternative drugs with comparable effectiveness are available.

C. Governance: strengthening institutions, law, and policy

- **Coordination and Synergies**
  Improve coordination and realize synergies of ongoing initiatives at the international, regional and national level (e.g., the Joint UN Programme of Green Procurement in the Health Sector; the WHO programme on quality and safety of medicines; relevant SAICM initiatives, such as EDC Strategy, as well as other existing regional and national initiatives).

- **Industry consultation**
  Promote industry participation and responsibility.

- **Environmental standards**
  Derive limits/thresholds for ecotoxicological-relevant pharmaceuticals in surface waters.

D. Enhance capacity building and technical cooperation

- **Capacity building**
  Implement capacity building and technical cooperation to support developing countries and countries with economies in transition.

- **Monitoring and analytics**
  Establish monitoring campaigns, standardized protocols, and analytical capabilities to measure pharmaceuticals in environmental matrices at relevant concentrations.

E. Illegal international traffic

- **Addressing illegal traffic**
  Withdraw substandard, spurious, falsely-labelled, falsified, or counterfeit medical products from the world market.
7. References


www.pharmaceuticals-in-the-environment.org