SAICM/OEWG.2/INF/15

Distr.: General
6 October 2014

English only

Strategic Approach to International Chemicals Management

Open-ended Working Group of the International Conference on Chemicals Management
Second meeting
Geneva, 15–17 December 2014
Item 5 (b) of the provisional agenda*

Emerging policy issues and other issues of concern: new proposed emerging policy issue for consideration by the International Conference on Chemicals Management at its fourth session: environmentally persistent pharmaceutical pollutants

Submission on a nominated new emerging policy issue: environmentally persistent pharmaceutical pollutants

Note by the secretariat

The secretariat has the honour to circulate, for the information of participants, the final version of the submission by the Ministry of the Environment of Peru, the Ministry of Housing, Land Planning and the Environment of Uruguay and the International Society of Doctors for the Environment for a nominated new emerging policy issue on environmentally persistent pharmaceutical pollutants (see annex). The submission is reproduced as received by the secretariat, without formal editing.

* SAICM/OEWG.2/1.

Annex

Questionnaire for governments and organizations to nominate possible emerging policy issues for consideration by the International Conference on Chemicals Management at its third session	Strategic Approach to International Chemicals Management Please return **by 15 March 2014** to: SAICM secretariat 11–13 chemin des Anémones CH-1219 Châtelaine, Geneva Switzerland Tel: 41 22 917 86 31 Fax: 41 22 797 34 60 E-mail: saicm@unep.org
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State the problem

Pharmaceuticals comprise one of the few groups of chemicals specifically designed to act on living cells. Many Pharmaceutical chemicals are designed to be slowly degradable or even non-degradable, to resist chemical degradation during passage through the human or animal body. Thereby, they present a special risk when they or their active metabolites or degradants enter, persist, and disseminate in the environment.

In this proposal, we use the term EPPP (Environmentally Persistent Pharmaceutical Pollutants) as an abbreviation for these substances.

Although Pharmaceutical residues entering the environment are included in Directive 2001/83/EC (as amended), Directive 2001/82/EC (as amended) they are insufficiently addressed in developing countries as a pollution problem.

A new global database on measured environmental concentrations with more than 120,000 entries has shown that EPPPs have become a global problem with potentially harmful concentrations for aquatic organisms found in all UN regions ().
Chemicals of pharmaceutical origin, widely used globally by humans and for food production for an intended purpose they can persist in the environment and residues are presently found in drinking water. They are found in fish and other animals where they may accumulate.

Pharmaceuticals reach the environment mainly in three ways:
- Manufacturing plants producing the active substances may release pharmaceuticals into the aquatic environment.
- Humans and animals treated with pharmaceuticals excrete residues, intact or metabolized, into their urine and faeces, from which they pass into sewage treatment plants or directly into the environment. Sewage treatment plants often have no specific procedures to eliminate EPPP.
- Unused or expired pharmaceuticals may be disposed from households or hospitals and reach the environment, either via sewage water or via urban solid waste handling.

With the exception of downstream sewage plants receiving water from pharmaceutical industries (where large amount of pharmaceutical chemicals have been monitored), the concentrations of active residues of chemicals of pharmaceuticals origin detected in surface waters and sediments may be low but they may persist for long periods of time contributing to chronic and persistent exposure .

They may pose a threat of important magnitude for Public Health with significant adverse effects on the environment and on human health as exposure may start since conception during the phases of development, with possible important consequences for adult life, e.g. special impacts on vulnerable populations (elderly, sick, and children).

As described above, EPPPs are already found in water all over the world. That diffuse exposure might contribute to:

- endocrine disruption,
- development of microbes resistant to antibiotics,
- reproductive effects that may derive on extinction of species and imbalance of sensible ecosystems,
- genetic, developmental, and immune health effects in humans and other species.

As the world’s population is growing and ageing, more people in the developing world can afford medical treatment, and as new treatments are developed, the degree of environmental pollution from chemicals of pharmaceutical origin can be expected to increase without further developing adequate risk management measures. Thus, to mitigate current and to prevent future problems, recognition and global management actions have to be established.

Information that can be used to assess the nominated issue

a) Magnitude of the problem and its impact on human health or the environment taking into account vulnerable populations and any toxicological and exposure data gaps

Chemicals of pharmaceutical origin present in the environment are a global issue. This has recently been demonstrated by a database on the worldwide occurrence of chemicals of pharmaceuticals origin in the environment (http://www.pharmaceuticals-in-the-environment.org/en/home/dok/2.php). The database covers at least 71 countries in all five UN regional groups. It indicates that in total 631 different chemicals of pharmaceutical origin (or their transformation products) have been detected in the environment, including antibiotics, analgesics, lipid-lowering drugs, estrogens, and many other therapeutic groups.

Most chemicals of pharmaceuticals origin have been detected in surface water and sewage effluent, but also in other environmental matrices, including groundwater, tap water/drinking water, manure, and soil. According to the database, sixteen different chemicals of pharmaceuticals origin are found in surface water, groundwater, and/or drinking/tap water in each of the five UN regional groups. In many countries, certain these chemicals of pharmaceuticals origin prevail at concentrations above established Predicted No-Effect Concentrations (PNEC) mainly in surface waters, suggesting adverse eco-toxicological effects on organisms and microorganism at these locations. Urban wastewater discharge is the dominant emission pathway, while discharge from manufacturing, animal husbandry, and aquaculture are important regionally.

Chemicals of pharmaceuticals origin have adverse effects on the environment and biodiversity. Therapeutic levels of the hormone levonorgestrel have been found in rainbow trout downstream from a sewage plant. In a whole lake experiment, male fish exposed to synthetic oestrogen at concentrations found in polluted environments became feminized and within seven years were almost extinct, with downstream effects on the entire ecosystem. The antidepressant oxazepam alters behaviour and feeding rate of the wild fish species Perca fluviatilis at environmentally relevant concentrations, so that antidepressants in surface water may alter animal behaviours that are known to have ecological and evolutionary consequences. Livestock excrements containing residues of antiparasitic macrocyclic lactones have shown to affect dung fauna resulting in reduced degradation rates. Antibiotics reduce growth of plants and are toxic to photoautotrophic aquatic organisms. The anti-inflammatory drug diclofenac has been shown to cause kidney failure and death of Indian vultures feeding on livestock treated with the drug, leading to a significant decline in the Indian vulture population.

The impact of chemicals of pharmaceutical origin in the environment on human health cannot be clearly demonstrated yet. Based on the current level of scientific information, adverse impacts of the environmental exposure to chemicals of pharmaceutical origin present in the environment on human health are unlikely, as concentrations of chemicals of pharmaceuticals origin present in drinking water are generally below minimum therapeutic doses, although locally high concentrations to these chemicals occur in well water used as drinking water. Uncertainties prevail regarding the risks of low-level chronic exposure in humans, exposure from conception, during childhood, reproductive age and in other vulnerable population (third age as well as in health conditions) due the presence of chemical of pharmaceutical origin in drinking water.

There is a gap of knowledge regarding the multiple chemical exposures (additive, synergistic or antagonistic effects) to chemicals of pharmaceutical origin as well as of multiple exposures with other pollutants concurrently present in surface and drinking water. There is a scarcity of systematic monitoring schemes. Increasing prevalence of antimicrobial resistance shows how the emission of antibiotics into the environment may have direct negative health consequences for human health and veterinarian.

The presence in the environment of chemicals of pharmaceuticals origin poses an increasing problem. As the world's population is ageing, the production, use and disposal of pharmaceuticals products are growing as well the demand of pharmaceuticals in food production and veterinarian uses. The degree of environmental pollution from chemicals of pharmaceuticals origin can thus be expected to increase, unless adequate global preventive measures are introduced.

State of the knowledge:

i) ***Pharmaceuticals are special kind of chemicals***. They are manufactured to be biologically active in living organisms and to have long half-lives. This makes them more risky when released into in the environment where they can impact nature.

ii) The levels of ***pharmaceuticals in surface or drinking water*** are generally below 1 mg per litre, often measured in 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 a DDD (defined daily dose) of 10 mg implies that a volume of 100,000 litres 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 chronic exposure to concentrations of pharmaceuticals*** in the water or the ***vulnerable population exposure for example since conception during the period of development.***

iii) ***Aquatic organisms may bio-concentrate and bio-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 biphenyls, a group of industrial chemicals earlier used in, for example, building materials). The same mechanism may also be applied for chemicals synthesized for pharmaceutical uses.

Bioaccumulation of citalopram (SSRI, antidepressant) and propoxyfen (painkiller) has been found in perch in the Baltic Sea. Therapeutic levels of levonorgestrel (a sex hormone) have been found in Rainbow trout downstream from a sewage plant.

iv) ***Pharmaceutical chemicals are not conceived or designed to enter in the environment and persist there but rather are developed for a clear pharmaceutical purpose.*** Pharmaceuticals are synthetic chemicals. They belong to a wide group of different chemical families and may also react differently in the environment. 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 during periods of development, on aquatic microorganisms or how they may affect other animals.*** Based on this, the persistent and ***diffuse exposure to low doses of pharmaceutical synthetic chemicals, for long periods of time, is not well known or studied.***

v) ***The diffuse dissemination of the EPPP in the environment may indiscriminately expose vulnerable populations: embryos/foetuses, children and adolescents, men and women of reproductive age, and elderly persons.*** Some of the pharmaceuticals found in surface water are prescribed to patients under special controlled conditions for short periods of time due to the risk of side effects. Others are prohibited from prescription to pregnant women or children. These chemicals were not synthesized to expose the general population in a diffuse manner. This presents a new and emerging issue under chemical safety and global pollution.

vi) ***A large proportion of excreted or disposed medicines reach the public sewage treatment plants***. Today, most sewage plants do not have the capacity to ensure that the treated water does not contain pharmaceutical chemicals. This is sometimes also the case for the industries' own sewage plants. In many parts of the world, effluent sewage plant water is reused as drinking water or as irrigation water for food crops, whereas it may, not always be usable after sewage treatment. Detection and monitoring on a global scale of EPPPs in drinking and surface water, as well as in animals and plants, is necessary to understand the magnitude of the problem, as shown by the global database.. The first step is to recognize EPPP as an emerging issue to be able to invest the necessary human and financial resources and develop effective environmental detection methods and monitoring strategies.

b) Extent to which the issue is being addressed by other bodies, particularly at the international level, and how it is related to, complements or does not duplicate such work.

The issue of chemicals of pharmaceutical origin present in the environment is currently insufficiently addressed at the international level. However, due to the global and interdisciplinary scope of the problem, international coordination is needed.

Initiatives at the international level include activities conducted by the WHO, the joint UN project on sustainable procurement of pharmaceuticals, and SAICM. WHO has conducted activities that address the issue of chemicals of pharmaceutical origin present in the environment to a certain extent, including the WHO Pre-qualifications Programme on Quality and Safety of Medicines, the Member State Mechanism on Substandard/spurious/falsely-labelled/ falsified/counterfeit medical products and the Global Strategy for Containment of Antimicrobial Resistance. Moreover, chemicals of pharmaceutical origin present in the environment have been addressed to varying degrees in WHO reports and guidelines on health care waste management, and the assessment of health risks of pharmaceuticals in drinking water..

In Europe, the joint UN project (UNDP, UNEP, UNFPA, UNOPS, and WHO) aims to improve the sustainability of the procurement procedures of UN agencies and criteria for health products and services, and thereby to diminish possible future negative environmental effects of pharmaceuticals. Two different approaches to reach the target are being undertaken: (i) to develop and implement WHO evidence-based technical guidelines on sustainable procurement of health care products including pharmaceuticals, thereby creating an incentive for manufacturers to strive towards production of more "green" products, and (ii) to integrate environmental criteria into Good Manufacturing Practice (GMP) utilized by WHO to pre-qualify medications for procurement.

The SAICM initiative on endocrine disrupting chemicals partially overlaps with the issue of chemicals of pharmaceuticals origin in the environment, as some pharmaceuticals (e.g. hormones and contraceptives) have endocrine disrupting properties.

In a recent workshop in Geneva, Switzerland, in April 2014 and organized by the German Federal Environment Agency, international experts gathered to discuss the current state of knowledge on the issue of chemicals of pharmaceuticals origin in the environment as well as the results of a research project on the global occurrence of chemicals of pharmaceutical origin in the environment. The workshop summary is attached as supplementary information to this document.

On a national level, several countries have funded extensive research on chemicals of pharmaceutical origin in the environment (e. g. the United States, Canada, the European Union, or China). An environmental risk assessment of these pharmaceuticals chemicals is required in e. g. the US and the EU. This is partially harmonized via VICH (International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products). On a national and local level, initiatives to manage chemicals of pharmaceutical origin in the environment have started, such as the classification system of the Stockholm County Council or the Swiss programme to upgrade large sewage treatment plants.

c) Gaps to be addressed:

Existing knowledge and perceived gaps in understanding about the issue

Existing knowledge gaps in understanding about the issue of chemicals of pharmaceutical origin in the environment relate to the risks of early (since conception) and low-level chronic exposure in humans when present in drinking water or bio-concentrate in food. Moreover, uncertainties prevail regarding the combined (additive, synergistic or antagonistic) effects of environmental chemical multiple exposures (synergistic effect).

Understanding the behaviour, fate, and effects of chemicals of pharmaceutical origin in the environment should be further developed, especially for the ones which are wide spread used, are highly toxic, have been on the market for several years/decades and/or are diffuse pollutants.

Furthermore, the scarcity of environmental systematic monitoring programmes, lack of standardized, harmonize and comparable sampling system according to established analysis protocols as well as regional capacity to support multi-centric studies should be addressed.

There are currently no test methods to assess whether negative effects may occur after long term environmental diffuse exposure in humans, since conception and during the vulnerable period of development, on aquatic microorganisms, or how they may affect other animals. Consideration must be given to bioaccumulation in fish and other aquatic food used by humans. Therefore, the precautionary principle must be guiding.

Another important gap to be addressed is the importance to design pharmaceutical chemicals with consideration of their environmental fate, i.e. provide for degradation in the environment, exclude formation of active metabolites and degradants, others.

d) Extent to which the issue is of a cross-cutting nature

The global problem posed by the pollution of surface water (as well as groundwater, drinking water, tap water, and to some extent farmland and soil), with chemicals of pharmaceuticals origin and their residues is well-known to scientists in the field.

Pharmaceuticals are synthetic chemicals belonging to a wide group of different chemical families and may also react differently in the environment as are not conceived or designed to enter in the environment. As there are thousands of different synthesized chemicals present at the same time in the environment, different interactions may occur and the result of these multiple exposures in humans and to nature are not sufficiently studied or understood.

Documented evidence shows that some pharmaceuticals enter and persist in the environment.

Little is known on the possible negative effects and impacts of EPPP in humans and the environment by diffuse and systematic exposure, for long periods of time, especially during the vulnerable periods of development.

The issue of chemicals of pharmaceutical origin in the environment is of a cross-cutting nature, as it encompasses both the issue (among others) of antibiotic resistance and endocrine disruptors.

Chemicals of pharmaceuticals origin in the environment (as antibiotics designed to kill bacteria and viruses) can increase risks of antimicrobial resistance. The presence of antimicrobials in the gut of humans and animals leads to the development of resistant bacteria and resistance genes that can be excreted in faeces and spread to wastewater, sludge, manure, and soil. Resistance genes can also spread through the food chain, for example via human consumption of animals treated with antibiotics. Resistance genes can also develop in the environment if chemicals with antibiotic activity are present in the environment. The resistance genes from the increasing environmental reservoir can then be transferred to pathogenic bacteria. There is also evidence of an exchange of resistance genes between environmental bacteria and clinical isolates. The issue of antibiotic resistance is addressed for example by the World Health Organization (WHO).

Moreover, some chemicals of pharmaceutical origin in the environment have hormone activity (synthetic hormones) with endocrine disrupting potentials. In a whole lake experiment, male fish exposed to synthetic oestrogen at concentrations found in polluted environments became feminized and within seven years were almost extinct, with effects on the entire ecosystem. The issue of endocrine disruptors is addressed by SAICM. These may affect microorganism and wild life in severe and unexpected ways.

e) Information on the anticipated deliverables from action on the issue:

Greater visibility and policy engagement. Greater coordination, consistency and synergies between different initiatives around the globe engaging actors from different sectors.
Improved capacity for assessing and managing risks from EPPP, in particular in developing countries.
Particular outputs would include: Expert guidance for risk identification and assessment; priority setting for research and for risk management / control actions; information exchange and networking from which scientists and policy makers in developing countries and countries with economies in transition could especially benefit, resulting in greater understanding of the EPPP issues and of needs for priority actions.

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Describe the proposed cooperative action

With the objective of
- Raise awareness on EPPP as a global problem, its adverse effects on the environment and possible adverse effects on human health;
- Support the decision-making process;
- Reduce the introduction of chemicals of pharmaceutical origin in the environment promoting cost-effective and measurable prevention measures;
- Improve understanding of the risk posed by EPPP to human health and the environment
- Implement capacity building and technical cooperation to support developing countries and countries with economies in transition,
- Monitor EPPP in order to support decision making process, prioritization of actions, guidance and training tools / activities involving relevant expertise.
- Facilitate information exchange, discussion forums and mutual support in research and advice on translation of research results into control measures.

By
-Establishing an international project on EPPP by building on existing activities, in particular of European Commission, UN European Agencies (Project under UNDP, UNEP, UNFPA, UNOPS, and WHO) including the Swedish experience.
- Building synergy with the EDCs (endocrine disruptors) Strategy, as many actions are similar and points to similar actors
- Providing information on prevention tools for the manufacturing of pharmaceuticals, like chemical substitution or modification of processes (Cleaner Production Management).
- Facilitating information exchange and networking, inter alia through regional and sub-regional workshops / discussion forums and a dedicated website that links to relevant information sources.
- Providing international support activities to build capacities in countries, in particular developing countries and countries with economies in transition,
- Creating an international network of scientists, risk managers, and others that are particularly concerned with EPPP issues
- Improving coordination and consolidation of ongoing initiatives at the international, regional and national level, improve use of available resources
- Building synergies between, but not limited to the Joint UN Programme of Green Procurement in the Health Sector; WHO programme on quality and safety of medicines; relevant SAICM initiatives (as EDCs Strategy) as well as other existing regional and national initiatives.