Strategic Approach to International Chemicals Management

Nomination of emerging policy issues for consideration by the International Conference on Chemicals Management at its third session

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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 30 November 2010** 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
Issue Environmental Persistent Pharmaceutical Pollutants (EPPP)	**Submitter** **ISDE -International Society of Doctors for the Environment** Contacts: **Ingrid Eckerman**, Swedish Doctors for the Environment (LfM), Statsrådsvägen 11, 128 38 Skarpnäck, Stockholm, Sweden. ingrid.eckerman@lakareformiljon.se. www.lakareformiljon.se **Cathey Falvo**, International Society of Doctors for the Environment, ISDE - President elect, 1325 NW 21 Terrace, Delray Beach FL 33445, USA, cathey.falvo@gmail.com **Lilian Corra** International Society of Doctors for the Environment, ISDE - International Secretary. Santa Fe 3435, 1A Ed 2. Buenos Aires. Argentina CP 1425. lcisde@arnet.com.ar

State the problem

Pharmaceuticals chemicals, widely used globally by humans and for food production for an intended purpose, may enter and persist in the environment during their life cycle creating a new and emerging problem that is still not properly generally recognized and may pose a threat of important magnitude, with significant adverse effects on environment and human health and special impact in vulnerable populations.

Environmental Pharmaceutical Persistent Pollutants, EPPP, are insufficiently addressed as not covered by other international or regional agreements or arrangements.

As the world's population is growing and welfare is increasing, the use of pharmaceuticals is rapidly increasing. Pharmaceuticals chemicals entering the environment persist there and residues are presently found in drinking water. They are found in fish where they may accumulate. The presence of different pharmaceutical chemicals contributes to the increasing multiple chemical cocktail that today's population is exposed to. Vulnerable populations are exposed, for example foetuses during the windows of development, with possible important consequences for life.

The effect that the chronic exposure to environmental pharmaceuticals chemicals adds to the effects of other chemicals in the cocktail is still not studied. The different chemicals might be potentiating synergistic effects (1+1=3).

Environmental Persistent Pharmaceutical Pollutants (EPPP) are already found in drinking water all over the world. The diffuse exposure might contribute to
- extinction of species, imbalance of sensible eco-systems
- genetic, developmental, immune and hormonal health effects to humans and other species
- development of microbes resistant to all antibiotics and other undesirable effects.

Pharmaceuticals comprise one of the few groups of chemicals specifically designed to act on living cells, which presents a special risk when they enter, persist and disseminate in the environment. Pharmaceuticals chemicals are designed to be non-degradable to resist the acid environment in the stomach, and to be long-lasting; to be administrated according to a specific defined time schedule.

Pharmaceuticals reach the environment mainly in three ways:
- They are excreted from humans and animals, intact or metabolized, mainly into the urine, passing on to the environment directly or via sewage plants.
- Unused reach the environment either *via household water* or via urban solid garbage handling.
- Manufacturing plants producing the active substances might unintentionally release pharmaceuticals into the environment.

Some pharmaceuticals are degraded to various extents in sewage treatment plants, but others leave the plant in active forms. Active residues of pharmaceuticals have been detected in surface water, and they may persist in the environment for long periods of time. Large amounts of antibiotics and other pharmaceuticals have been found downstream from sewage plants for pharmaceutical industries. EPPPs from sewage sludge used as fertilizer are absorbed by soya, and antibiotics have been found in the leaves.

Which EPPPs are found in drinking water depends on what resources and detection methods are available. Atenolol (beta blocker), citalopram (antidepressant drug), diclofenak (analgesic), ibuprofen (analgesic), metoprolol (beta blocker), naproxen (anti-inflamatory) and trimetoprim (antibiotic) have been found in drinking water of Stockholm, Sweden. Fish caught downstream from the sewage plants of Stockholm contain EPPPs like citalopram (antidepressant drug) and propoxyphene (narcotic/anesthetic). Several broad-spectrum antibiotics in very high concentrations, as well as bacteria resistant to all known antibiotics, were found downstream from a sewage plant in India. Also in Indian drinking water cetirizin (antihistaminic), ciprofloxacin (antibiotic), enoxacin (antibiotic), terbinafin (antimycotic), and citalopram (antidepressant drug) were found. Up to 14 different pharmaceuticals have been found in the drinking water of big cities around the world. There also exist publications reporting the presence of cancer drugs in surface water in some countries.

Some of these environmental pharmaceuticals chemicals are well known to have serious genotoxic effects in humans. Many are not very well studied for their toxic effects on human periods of development. A majority of these pharmaceuticals chemicals present an environmental halftime longer than one year. Serious effects of EPPPs on water-living organisms, especially on reproductive systems, have been already shown as well as on microbial communities.

The concentrations of pharmaceuticals chemicals in drinking water are so far very low, but will increase due to increasing use of pharmaceuticals. The tendency of bio-accumulation in fish is alarming, as fish is very important nourishment.

The impact of pharmaceuticals chemicals, due to diffuse exposure by their presence in the water environment, will contribute to the wide chemical exposure of all species and to their possible extinction, as well as the imbalance in sensitive eco-systems.

Consequences for human health and the equilibrium of the biological environmental system may be irreversible and of great impact.

Multiple human exposures to EPPP may start at conception and may be combined with a cocktail of other chemicals present in the environment. The effects of exposure to these mixtures are difficult to understand due the complexity of the situation during a period of special vulnerability and sensitivity, but can not be denied. Another very serious threat is development and spread of bacteria, viruses and other microbes resistant to the antibiotics present in the environment, with possible unpredictable important consequences.

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

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[1]) 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 during the period of development.***

i) ***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 biphenils, a group of industry chemicals earlier used in e.g. building materials). The same mechanism may also be applied for chemicals synthesized for pharmaceutical uses.

ii) ***Pharmaceutical chemicals are not thought or designed to enter in the environment and persist there but for a clear pharmaceutical purpose.*** Pharmaceutical 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, it's pharmacological and toxicological effects is 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 human, during periods of development, on aquatic microorganism or howthey 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 currently well know or studied***. As there are thousands of different synthesized chemicals present at the same time in the environment, different interactions may occur that are not sufficiently studied or understood.

iii) ***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 or weak persons.*** Some of the pharmaceuticals found in surface water are prescribed to patients under special controlled conditions for short periods of time due 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 the chemical safety global pollution.

iv) ***It can be assumed that a large portion of excreted or disposed medicines reach the public sewage treatment plants (STP's) although at the present quantitative data of the global pollution are not available***. Alternatively, the sewage is directly let out into various surface waters like rivers, lakes, streams or the open sea. Detection and monitoring at global scale of EPPPs in drinking and surface water as in animals is necessary to understand the magnitude of the problem. 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.

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

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.

Environmental Pharmaceutical Persistent Pollutants, EPPP, are insufficiently addressed as not covered by other international or regional agreements or arrangements.

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***.

In the European Union, the new directive for human pharmaceuticals (2004) explicitly requires that all member states should establish collection systems for unused or expired medicines. This directive does not cover disposal or destruction, for example disposal into the sewage system is still a legally accepted route of elimination.

For pharmaceuticals approved for marketing in EU 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.

c) Existing knowledge and perceived gap in understanding about the issue

Examples showing the presence of pharmaceuticals in water and in animals:

Below are some examples that illustrate the state of the science of this important emerging problem.

Estradiol (estrogen, synthetic hormone)
Concentrations in surface water alone are not sufficient to assess the risk of negative environmental effects of this synthetic hormone in the aquatic environment as is an endocrine disruptor. Thus, estrogenic compounds like ethinyl-estradiol (estrogen hormone) 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 sewage treatment plant (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.

Gemfibrozil (cholesterol and triglycerides lowering drug) 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 propanolol was found to cause a significant decrease in egg production in medaka fish, at a concentration close to that demonstrated in the sewage treatment plants (STP) effluents. Gemfibrozil (cholesterol and triglycerides lowering drug) 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.

Citalopram / Fluoxetine (serotonin reuptake inhibitor anti depressants, SSRI's)
Some SSRI's have been shown to accumulate in exposed fish. Citalopram has been detected in liver from wild perch in low µg 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 still unknown.

Antibiotics
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 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. When entered into the environment they are poorly degraded in nature. They can be toxic to other animals, affecting particularly microorganism and 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).

Oseltamivir (antivirus use to treat H1N1 influenz) 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.

Gaps

- Effective environmental detection methods have to be developed and global detection strategy applied to map the current global situation.
- There are currently no test methods to assess whether negative effects may occur after long term environmental diffuse exposure in humans, during of the vulnerable periods of development, on aquatic micro-organism or how may affect other animals.
- Concentrations in surface water alone are not sufficient to assess the risk of negative environmental effects of these synthetic chemicals.

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

Environmental Pharmaceutical Persistent Pollutants, EPPP, are not thought or designed to enter and persist in the environment. Pharmaceutical are synthetic chemicals belonging to a wide group of different chemical families and may also react different in the environment.

There exist very well documented evidence that some pharmaceutical enter and persist in the environment, some are endocrine disruptors (synthetic hormones), and some are designed to kill bacteria and viruses (antibiotics) and may affect microorganism and wild life in severe and unexpected ways.

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.

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 exposure in human and nature are not sufficiently studied or understood.

Describe the proposed cooperative action

a) Dissemination of information through the secretariat's clearing house function or other mechanism

- Involve different sectors to create awareness on this important emerging issue
- Help to improve the public recognition of pharmaceuticals as chemical environmental pollutants, with possible important negative effects on environment, biodiversity and human health.
- Help to include all important sector involved in this emerging issue
- Help to disseminate the existing information and to identify new emerging information and partners already working in the issue

b) Recommendations for the Conference which could include requests for actions addressed to the governing bodies of international organizations, Governments, scientific bodies, civil societies stakeholders and private sector

- Inclusion of EPPP as one of the emerging issues for ICCM3
- Inclusion of Environmental Pharmaceuticals Persistent Pollutants, EPPP, in the SAICM Global Plan of Action
- Recommend the main actors to get involved and become leaders in this new and emerging issue, inviting for example WHO to lead the actions.
- Invite scientific and health bodies and other main private sector and civil society actors to engage and recognize this important issue

c) Initiation of follow up work under the auspices of the Conference, including through inter-sessional work at regional meetings, workshops training sessions, internet-based consultations, teleconferences, work by subsidiary bodies, the secretariat or other mechanism

At ICCM 3:

- Convene the parties for a one day workshop on EPPP at ICCM3
- Indentify and invite scientist and researchers experts to expose on the current state of science on EPPP
- Indentify and invite experts on chemical safety polices to expose on the current state of the art of polices at global, regional and national level
- Prepare a document or statement to highlighting the importance of the EPPP and call for action
- Promote the organization of a multi-sectorial working group to keep the work going inter-sessionaly and presenting the results of the advances to the next conference

Inter-sessional work:

- Maintain the links with the EPPP ad hoc Working Group
- Present the discussion and dissemination of already existing information on EPPP and promote the identification of experts at the regional level to complete the global picture
- Promote capacity building by including all sectors involved to install the discussion
- Open a discussion forums by using internet based interactive mechanism (for example Twiter, Facebook, Fss) to promote the participation, dissemination and identification of the state of the situation
- Prepare a document to report on the state of the science and technology, global pollution situation, possible effects on health and the environment and recommendations for actions to be presented to the parties at ICCM4

Different task of this WG on EPPP:

- *Include representatives of all sectors involved with special emphasis in science/technology/health/private/ policy and community interest sectors*
- *Science and technology:*
  - Review of the already existing information on:
    - Presence of pharmaceutical chemicals in the environment
    - Monitoring of the presence of pharmaceuticals chemicals in surface and underground water
    - Monitoring of the presence of pharmaceutical chemicals in wildlife
    - Persistence of pharmaceutical chemicals in the environment
    - Human health an the environment effects of the persistent diffuse long term exposure to EPPP
    - Identification of vulnerable population and populations at risk among humans but also in the environment
    - Identify the science and technology existing gaps and promote research to fulfil them
- *Regulatory framework*:
  - Identification of existing regulations or mechanisms to control EPPP emissions to the environment (survey including also national experiences)
  - Explore possible articulation mechanisms with other partial regulations when existing
  - Promote the discussion to define and implement regulations at global level
  - Explore the already existing regulation on the information of the persistence of the pharmaceutical synthetic chemicals on the environment
  - Identification of the already existing limits for pharmaceutical chemicals in drinking and surface water and the reason this limits were adopted in relation of the protection of human health and the environment.

d) Specific commitments by Governments, civil society, intergovernmental organizations and private sector, such as international work or partnership

- *Possible main partners may be:*
  - World Health Organization under Public Health and the Environment
  - UNEP Chemicals
  - Government of Sweden, EPA - USA, UK
  - ISDE, Collegium Ramazzini
  - ICCM and other pharmaceutical chamber producers

e) Relevance, as appropriate, to the Global Plan of Action and the Strategic Approach Overarching Policy Strategy or other mechanism for providing capacity building to proponers.

- This proposal is under the framework of the **Dubai Declaration**
- Relevance to the **Overarching Policy Strategy**

EPPP is a relevant global issue under the scope of the SAICM-OPS as affects environmental and health aspects of chemical safety. Pharmaceutical chemicals become undesirable pollutants when present in the environment. Environmental Pharmaceutical Persistent Pollutants represents a new and emerging issue that pose a problem of important magnitude for human health and the environment. EPPP are not regulated by domestic food or pharmaceutical authorities or arrangements.

- **Relevance to the Global Plan of Action**

To recognize EPPP as a new and emerging issue and being able to include them in the SAICM-GPA will target a new topic not currently addresses in existing agreements and work areas.

EPPP clearly may be classified as Persistent Bio-accumulative and Toxic Substances (PBTs), some of them with endocrine disruption and genotoxic characteristics, that may affect reproductive, endocrine, immune an nervous system, affecting human health and the environment.