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:

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Issue

Environmental Persistent Pharmaceutical Pollutants (EPPP)

Submitter

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State the problem

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. In this paper, we suggest the term Environmental Pharmaceutical Persistent Pollutants, EPPP. EPPP are insufficiently addressed as not covered by other international or regional agreements or arrangements.

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, and may pose a threat of important magnitude, with significant adverse effects on environment and human health and special impact in vulnerable populations.

As the world's population is growing and ageing, more people can afford medical treatment and new treatments are developed, the amounts of pharmaceuticals can be expected to increase rapidly. 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.

With exception for downstream sewage plants, the concentration of pharmaceuticals in water is probably extremely low. However, 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). An extremely sensitive group in this respect are foetuses.

Environmental Persistent Pharmaceutical Pollutants (EPPP) are already found in water all over the world. The diffuse exposure might contribute to

- **extinction of species and imbalance of sensible eco-systems, as many EPPS affect the reproductive systems of for example frogs, fish and mussles;**
- **genetic, developmental, immune and hormonal health effects to humans and other species, in the same way as e.g. oestrogen-like chemicals;**
- **development of microbes resistant to antibiotics, as is found in India (1) .**

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. Half-life in nature varies depending on the environment (air, water, soil, sludge), but is more than one year for several compounds (2, 3). Clofibric acid, a metabolite of the lipid-lowering agent clofibrate, can still be found in surface as well as well water, although clofibrate long ago has been withdrawn. Concentrations of EPPPs can vary from 1 ng to 1 mg per litre (2). Serious effects of EPPPs on water-living organisms, especially on reproductive systems, have been already shown, as well as on microbial communities (4, 5, 6, 7).

Concentrations in surface waters, groundwater and partially treated water are typically less than 0.1 µg/l (or 100 ng/l), and concentrations in treated water are generally below 0.05 µg/l (or 50 ng/l).(ny 8 WHO) However, all water on the earth is part of the same stable pool, and as larger amounts of pharmaceuticals are consumed, there is a risk that the concentration of pharmaceuticals in drinking water will increase. The tendency of bio-accumulation in fish is alarming, as fish is an important nourishment.

The impact of pharmaceutical chemicals, due to diffuse exposure by their presence in the water environment, might contribute to the wide chemical exposure of all species and to their possible extinction, as well as to the imbalance in sensitive eco-systems. Consequences for human health and the equilibrium of the biological environmental system may be irreversible.

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

i) ***Pharmaceuticals are special kinds of chemicals***. They are manufactured to be biologically active in living organisms, to be persistent to biodegradation and to have long half-lives. This makes them more risky in nature. Release is ongoing always and everywhere, diffuse and impossible to control. They cannot be forbidden.

ii) The levels of ***pharmaceuticals in surface or drinking water*** are generally below 1 mg per litre, often measured in ng per litre (2, 8). 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) 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.***

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 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. Bioackumulation of citalopram (SSRI, antidepresssivum) and propoxyfen (painkiller) has been found in perche in the Baltic Sea. Therapeutic levels of levonorgestrel (a sex hormone) has been found in Rainbow trout downstream a sewage plant (9).

iv) ***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 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 currently well know 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 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.

vi) ***It can be assumed that a large portion of excreted or disposed medicines reach the public sewage treatment plants (STP's)*** . Today, the sewage plants do not have the capacity to clean the water from pharmaceutical chemicals. This is sometimes also the case for the industries' own sewage plants. In many parts of the world, the sewage plant water is reused as drinking water, not always after cleaning treatment. To add a step for cleaning sewage water from pharmaceuticals means more energy, more chemicals and higher costs. - 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 and plants 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.

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 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.

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 in the aquatic environment. Synthetic hormones are endocrine disruptors. 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.

Cardiovascular medicines
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. There are several examples: In India, bacteriae resistant to ciprofloxacin have been found downstream pharmaceutical plants, genes for multi resistance were found in drinking water, and multi resistant Salmonella in water sprayed on vegetables. From Europe we know about the epidemic with multi resistant EHEC in summer 2011, originating from water sprayed vegetables.

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. 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 influenza) 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 reach environment also from cattle-breeding. A number of antibiotic compounds, as well as an insect repellent, DEET, used in herd health programs on dairy farms have been shown foot printing into extensive aquatic environments.

Personal-care products
Synergetic effects on algae by a mixture of pharmaceuticals and personal-care products have been observed.

Environmental classification of pharmaceuticals
In Sweden, the industry together with universities and health care sector has developed a method for environmental risk assessment and environmental classification of drugs (10, 11). Environmental risk refers to the risk of toxicity to the aquatic environment. It is based on the ratio between predicted environmental concentration of the substance (PEC) and the highest concentration of the substance that does not have a harmful effect in the environment (PNEC). Environmental hazard expresses the inherent environmentally damaging characteristics of the substance in terms of persistence, bioaccumulation and toxicity. The toxicity tests used are acute toxicity of fish, acute toxicity of Daphnia sp. and growth inhibition test of algae. Most medications on the Swedish market are now classified. This gives the health care possibilities to make better choices when prescribing medicines.

Good manufacturing practice
"Good manufacturing practice" or "GMP" are practices and the systems required to be adapted in pharmaceutical manufacturing, quality control, quality system covering the manufacture and testing of pharmaceuticals or drugs including active pharmaceutical ingredients, diagnostics, foods, pharmaceutical products, and medical devices. The World Health Organization (WHO) version of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world. So far, emissions into the environment are not included.

Gaps

Effective environmental detection methods has 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. Therefore the precautionary principle must be guiding.

Concentrations in surface water alone are not sufficient to assess the risk of negative environmental effects of these synthetic chemicals. Consideration must be taken to bioaccumulation in fish and other acquatic food used by humans, as well as to additive and synergetic effects between pharmaceutical and other chemicals in the contaminated water.

In a small study, several pharmaceuticals were found in milk of goat, cow and human (12). More research is needed to find out how common this is, the concentrations and the sources.

The industry must be invited to actively work on reducing pharmaceuticals in the environment. Emission of pharmaceuticals should be included in GMP.

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

Environmental Pharmaceutical Persistent Polluants, 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), 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.

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Emerging contaminants in the Environment. USGS Toxic Substances Hydrology Program

These and other references are found on the webpage of Swedish Doctors for the Environment
http://www.lakareformiljon.org/index.php?option=com_content&view=article&id=151&Itemid=78

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 it 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 and nervous system, affecting human health and the environment.

The proposed actions can be summarized as follows:

The co-facilitators have drawn attention to the increasing but still low concentrations of pharmaceuticals in the environment and the evolving state of knowledge on potential environmental and health and safety risks. A range of cooperative actions is proposed, including raising awareness, sharing existing information and undertaking cooperative work. The attention of the Conference is drawn to the possible need to undertake intersessional work to explore issues relevant to developing countries and countries with economies in transition, and to a possible amendment to the Global Plan of Action of the Strategic Approach so as to include new work areas for pharmaceuticals.