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Comments on “Environmental Persistent Pharmaceutical Pollutants” as an Emerging Policy Issue for Consideration by the ICCM3

Submitted Issue

The International Society of Doctors for the Environment (ISDE) submitted “Environmental Persistent Pharmaceutical Pollutants (EPPP)” to the Strategic Approach to International Chemicals Management (SAICM) as an emerging policy issue for consideration by the International Conference on Chemicals Management at its third session (ICCM3). The Society of Environmental Toxicology and Chemistry (SETAC) has long been involved in developing and advancing the science on this issue. As a SAICM stakeholder since ICCM2, SETAC hereby offers the enclosed comments on the submitted issue. Our comments are prefaced by a summary of our relevant expertise.

SETAC Expertise

SETAC (www.setac.org) is a nonprofit, worldwide professional society comprised of individuals and institutions engaged in the study, analysis, and solution of environmental problems; the management and regulation of natural resources; environmental education; and research and development. SETAC's mission is to support the development of principles and practices for protection, enhancement, and management of sustainable environmental quality and ecosystem integrity. For more than 30 years, SETAC has promoted the advancement and application of scientific research related to contaminants and other stressors in the environment, education in the environmental sciences, and the use of science in environmental policy and decision-making. SETAC is unique among professional societies because all of our activities are structured to have balanced representation among academia, business, and government. This tripartite approach and emphasis on sound science affords SETAC work products an unparalleled degree of credibility. With more than 5,000 members in more than 100 countries, SETAC is truly global in scope.

SETAC has long been engaged on the subject of pharmaceuticals in the environment. A formally recognized forum with the society, the Pharmaceuticals Advisory Group (PAG), was established in 2005 to advance the science and understanding of pharmaceuticals in the environment. This group, currently consisting of approximately 200 members, is led by a tripartite steering committee and is open to all SETAC members as well as non-members. The mission of the PAG is as follows:

- Serve as a focal point within SETAC as means of involving the membership in research and discussions;
- Stimulate critical assessment in order to establish the best available science;
- Encourage the worldwide incorporation of the best available science and strategic approaches;
- Advance the overall understanding of the fate, effects, and potential environmental consequences of pharmaceuticals;

- Provide scientific support to ensure effective regulatory decision making;
- Provide a neutral platform and focal point for collaborative identification, evaluation, and resolution of scientific issues.

The PAG has organized a number of sessions at SETAC meetings where relevant science is disseminated. In Seville, Spain, in May 2010, the PAG organized a day-long session of experts to discuss the current state of the science on pharmaceuticals in the environment. The PAG is currently involved in organizing two workshops where invited international experts from academia, business, and government will meet to discuss and develop science-based solutions. The first workshop, held April 10-12 in Canada, aims to refine research priorities for understanding the impacts of pharmaceuticals and personal care products in the environment upon human and ecological health. The second workshop is being planned to investigate the topic of antimicrobial resistance. SETAC requires that the findings from workshops be disseminated to the public, so the outputs from these two events will have direct relevance to the EPPP issue.

Previous workshops SETAC has conducted that are relevant to the EPPP issue have resulted in two books: *Human Pharmaceuticals: Assessing the Impacts on Aquatic Ecosystems* and *Veterinary Medicines in the Environment* (www.setac.org; click on “Store”). In addition, our two journals, *Environmental Toxicology and Chemistry* and *Integrated Environmental Assessment and Management*, routinely publish peer-reviewed papers covering the fate and effects of pharmaceuticals in the environment, as well as practices and procedures for evaluating and managing their risks. Of particular significance are two open-access issues: Pharmaceuticals and Personal Care Products in the Environment, ET&C Volume 28, Issue 12, pages 2469–2753 (December 2009; <http://onlinelibrary.wiley.com/doi/10.1002/etc.v28:12/issuetoc>) and Environmental Risk Assessment of Pharmaceuticals (ERAPharm), IEAM Volume 6 Issue S1, Pages 511–613 (July 2010; <http://onlinelibrary.wiley.com/doi/10.1002/ieam.v6.1s/issuetoc>).

Drawing upon its expertise, the Steering Committee of SETAC Pharmaceuticals Advisory Group offers the following comments on the issue submitted by ISDE.

Comments on the submitted issue

The presence of pharmaceuticals in the environment has been recognized in recent years because analytical methods have been developed which are sufficiently sensitive to detect these substances. Pharmaceuticals have been identified to cause detrimental environmental effects in isolated, specific cases (e.g., the impact of the contraceptive 17α -ethinylestradiol on the gender distribution in fish populations, or the decline of vulture populations caused by the painkiller diclofenac). Thus, our awareness of pharmaceuticals as potential environmental contaminants has increased, although these substances have likely been present in the environment for a much longer time.

The SETAC PAG Steering Committee agrees with the ISDE statement that pharmaceuticals comprise a group of chemicals that is specifically designed to interact with living cells. However, unlike pesticides and biocides, only certain groups of pharmaceuticals are specifically designed to kill their target organism (e.g., antibiotics, antiparasitics, cytostatics). Other pharmaceuticals interact in more subtle ways with exposed organisms, including humans. In fact, SETAC’s PAG was chartered based on the premise that the complex interactions between pharmaceuticals in the environment, the multitude of potentially exposed organisms, and the intrinsically high bioactivity of pharmaceuticals warrant a reevaluation of the suitability of the existing environmental risk assessment science for pharmaceuticals.

The primary pathway for pharmaceuticals to enter the environment is through excretion after human and veterinary use. Human-use drugs and their metabolites in developed countries usually enter the environment after wastewater treatment (such as on-site or centralized collection and treatment systems), while veterinary medicines will often enter the environment directly after excretion. Other pathways from consumers to the environment include inappropriate “down the drain” disposal of unused medicines which may contribute to water concentrations and disposal in household solid waste, although this is believed to be a minor contributor to overall loadings. Manufacturing facilities may also discharge pharmaceuticals to the environment. At least in developed countries this pathway is generally well-controlled. High concentrations of antibiotics have been reported downstream of facilities in India. To date, the main focus of research has been on pharmaceuticals in surface waters resulting from releases from sewage treatment plants. However, pharmaceuticals have also been measured in groundwater assumed to be affected by private homeowner septic systems, by bank filtration, or by spreading of manure or sewage biosolids to agricultural land. In addition, unique pathways to the environment, unrelated to surface water discharges, also exist in certain circumstances, predominantly if not exclusively in developing countries. The most notable have had dramatic consequences, as exemplified by the severe effects on vultures in South Asia when they consumed carrion that had received therapeutic diclofenac before they died and were left to decompose.

A varying portion of most pharmaceuticals that enter a sewage treatment plant is removed from wastewater. The efficiency of removal strongly depends upon the technology and the individual pharmaceutical. Secondary (biological) treatment is effective in removing many pharmaceuticals to a significant degree. Generally, more advanced technologies, which are not yet in widespread use, especially in developing countries (e.g., ultrafiltration, reverse osmosis, ozonation), tend to remove a greater amount of most pharmaceuticals, though some pharmaceuticals are more difficult to remove (e.g., carbamazepine). Pharmaceuticals may also be present in biosolids and sludges that are byproducts of wastewater treatment, or in manure from farm animals treated with veterinary medicines. If these are used, for example, as land-applied soil amendments in an agricultural setting, such use can also lead to release of pharmaceuticals into the environment. Some drugs such as antiparasiticides are directly excreted into the environment by pasture animals. Antiparasiticides can be extremely toxic to non-target insects.

It is worth noting that the concentrations in drinking water reported by most studies can indeed be categorized as “trace,” that is, sub-microgram per liter (sub-part per billion) concentrations. Exposures via drinking water are even lower and many orders of magnitude less than therapeutic doses. This is not surprising. Only a fraction of the pharmaceuticals taken by humans or used in animal husbandry reaches the environment. Dilution, degradation, and removal by wastewater and drinking water treatment systems reduce the concentration even more. Nevertheless, some concern exists about the potential effect on humans of pharmaceuticals in drinking water, because sensitive sub-populations may be exposed (e.g., infants), the exposure can be chronic, and exposure may be to a variety of different pharmaceuticals whose combined effect is not understood.

Several studies currently suggest that drinking water that may contain trace levels of pharmaceuticals does not appear to cause adverse effects in people. These investigations include experiments in which animals have been exposed to drinking water that contains trace levels of pharmaceuticals and epidemiological studies that examine the incidence of adverse effects in communities using potable water containing trace levels of pharmaceuticals. Virtually all of these risk assessments have predicted or reported no adverse effects associated with trace levels of pharmaceuticals (though such studies have found links between adverse effects and other compounds that may be in drinking water, such as some disinfection by-products). Even acknowledging the limitations of these studies, the findings are encouraging from a human health

point of view and suggest that trace levels of pharmaceuticals in treated drinking water, as found in developed countries, are unlikely to cause adverse effects in humans according to current knowledge.

The most important cause for concern is the potential effect on aquatic biota, which is exposed to generally higher concentrations of pharmaceuticals, and several species have been shown to be extremely sensitive to some of the compounds. Many hundreds of papers have been published on adverse effects of pharmaceuticals on aquatic biota in laboratory settings. Some pharmaceuticals have also been tested in natural settings and have been shown to cause adverse effects. Perhaps the most notable is 17α -ethinylestradiol (the active ingredient in most birth control pills) applied to an experimental lake in Canada, which resulted in population-level impacts upon fish. High concentrations of this substance play a role in the feminization of male fish that has been reported from a number of countries across the world.

Depending upon their mode of action, different pharmaceuticals can be anticipated to affect different organisms and processes. In addition to the effects of 17α -ethinylestradiol on fish, some other examples include the detrimental effects of antidepressants upon reproduction of invertebrates, and effects of antimicrobials upon bacteria, algae, and plants. It is critical to understand how pharmaceuticals can affect not only individual organisms, but potentially populations, communities, and ecosystems; it is equally critical to understand the concentrations at which these effects could occur and whether or not such concentrations are likely in the environment. This requires going beyond short-term tests for acute toxicity to investigate chronic, long-term effects, using endpoints such as growth, reproduction, behavior and biodiversity.

As ISDE correctly notes, pharmaceuticals belong to a wide group of different chemical families and undergo different transformations in the environment. The form or activity of the drug in the environment can be drastically altered by such biotransformation and/or abiotic transformation processes. However, specific knowledge on transformation pathways in the environment and on the biological activity of most transformation products is rather rudimentary at the moment, which certainly constitutes a substantial knowledge gap.

Pharmaceuticals often do not fall under the classification as “persistent” or “bioaccumulative,” following standard classification schemes as suggested by OSPAR or REACH. Pharmaceuticals generally do not have the same extreme persistence and bioaccumulation properties as classical POPs (e.g., DDT and PCBs, the two examples cited by ISDE). However, some active ingredients are persistent and toxic and potentially also bioaccumulative. In addition, the production volumes of some pharmaceuticals and continuous release into the environment in sewage treatment plant effluent might lead to an almost constant concentration in surface waters. Pharmaceuticals have therefore been termed as being “pseudo-persistent,” although most undergo biodegradation. Based on current knowledge, pharmaceuticals do not seem to be subject to similar long-range transport as classic POPs.

Lastly, we note that some jurisdictions have implemented regulatory requirements on pharmaceutical manufacturers to evaluate the risks of their products for the environment. There are differences in these regulatory schemes concerning the concentration of a substance below which it can be assumed that risks are unlikely and further study is not warranted. However, despite such differences in the risk assessment approaches throughout the developed world, and the lack of assessment schemes in developing countries, there is an existing framework upon which improvements and harmonized approaches can be built. It must also be noted that regulatory requirements to evaluate risk often apply only to new products, while assessment of existing pharmaceuticals may occur only when a new use pattern or formulation is proposed.

In order to make maximum use of the limited resources available, approaches are needed for prioritizing further investigations, monitoring efforts, and assessments. In addition to monitoring, sound modeling approaches can be useful for prioritization, but additional work is needed in this area. More information on the fate of pharmaceuticals in treatment processes and the natural environment is needed, as traditional approaches to predicting fate processes may be inadequate for these substances. More robust evaluation of potential effects on non-target receptors and organisms (including use of information on mode of action and tests with non-traditional endpoints) and methods for evaluation of mixtures would all enhance the risk assessment process.

In conclusion, the issue of pharmaceuticals in the environment and the corresponding assessment of potential risks to human health and the environment are areas of ongoing scientific research. To date, most of the available information is from the developed countries and there is a lack of information for the developing countries. SETAC and in particular its pharmaceutical advisory group (PAG) would therefore welcome the opportunity to make a scientific contribution to the efforts of SAICM on this topic.

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