
International Conference on Chemicals Management

Fourth session

Geneva, 28 September–2 October 2015

Item 5 (b) (i) of the provisional agenda*

Implementation towards the achievement of the 2020 goal of sound chemicals management: emerging policy issues and other issues of concern: proposal on environmentally persistent pharmaceutical pollutants as a new emerging policy issue

Information submission from the United Kingdom of Great Britain and Northern Ireland on environmentally persistent pharmaceutical pollutants

Note by the secretariat

The secretariat has the honour to circulate, for the information of participants, draft information designed to guide the Hazardous Substances Advisory Committee of the United Kingdom of Great Britain and Northern Ireland in the event that it is asked to make a preliminary assessment on whether a human pharmaceutical is a pharmaceutical of environmental concern (see annex). The Hazardous Substances Advisory Committee is an independent expert scientific committee that provides advice to the Government of the United Kingdom on how to protect the environment, and human health through the environment, from potentially hazardous substances and articles, including nanomaterials. Further information can be found at www.gov.uk/government/policy-advisory-groups/hazardous-substances-advisory-committee. The document is reproduced as received by the secretariat, without formal editing.

* SAICM/ICCM.4/1.

Annex

How would HSAC characterize a pharmaceutical of concern regarding hazards in the environment?

Scope

This document is designed to guide the Hazardous Substances Advisory Committee (HSAC) if they are asked to make a preliminary assessment on whether a human pharmaceutical is or is not a 'pharmaceutical of concern' (PoC) in the environment. Veterinary medicines are not within the scope of this document nor is antimicrobial resistance (HSAC recognises that this issue is being considered by a number of other organisations). Individual pharmaceuticals rather than mixtures are addressed in this approach, although it is recognised that pharmaceuticals will exist in the environment in complex mixtures. The document is focussed primarily on the UK but it is accepted that data from other countries will be of use. The scope of this paper is primarily on rivers because that is where the vast majority of pharmaceuticals given to patients will ultimately end up.

This document is consistent with the principles of the HSAC paper "Considering Evidence: the approach taken by the Hazardous Substances Advisory Committee in the UK". Use of human pharmaceuticals will undoubtedly change with time and therefore an assessment performed now may not be applicable in the future. HSAC will revisit this document as required.

Introduction

There are about 3000 different human pharmaceuticals in use around the world, with between 1500 and 2000 of these being licenced for use in any one country. Relative to many industrial chemicals, the amounts used are small, nevertheless more than a ton consumed per year of an individual pharmaceutical would not be exceptional; a few are used at over a hundred tonnes per year. However, all pharmaceuticals possess biological activity, and some are extremely potent. Because people usually excrete a proportion of the parent, active molecule – the possibility exists that pharmaceuticals could enter the aquatic environment if they are not completely removed in wastewater treatment. In fact, several hundred different human pharmaceuticals have been detected in sewage treatment works effluents and rivers in many countries. Concentrations in rivers are low: a few ng/L is typical, with many pharmaceuticals probably being present at even lower concentrations than are currently possible to measure. Nevertheless, all aquatic organisms living in rivers will be exposed to a highly complex mixture of pharmaceuticals.

Much research is underway to determine whether or not any pharmaceuticals present in the environment pose a risk to the biota present in that environment. Regular claims are made in the scientific literature that pharmaceutical X is having adverse effects on some species or other at 'environmentally-relevant' concentrations. A very recent example would be the following paper: Niemuth, N.J. and Klapper, R.D. 2015. Emerging wastewater contaminant metformin causes intersex and reduced fecundity in fish. *Chemosphere* 135, 38-45. (Metformin is a very widely-prescribed anti-diabetic drug)

If HSAC was asked its opinion on whether or not it considered a pharmaceutical such as metformin to be of environmental concern, how would it go about answering that question? This brief paper suggests a procedure for doing so: the procedure involves taking a series of discrete, logical steps. The individual steps are presented below, followed by consideration of how HSAC applies them in forming an opinion.

Step 1: Assessing the existing literature to provide a first indication of the possible degree of concern

In this step, information from the scientific literature is collected and assessed (if available) on both the concentrations of the pharmaceutical in rivers and the concentrations reported to cause effects on aquatic species. No filtering of the literature is done at this stage, in order to achieve as unbiased an analysis as possible. Thus, the reported concentrations can come from any river, but preferably from within the UK. As an alternative or in combination with river measurements, data from consumption/wastewater discharge can be used to model the concentrations across Britain's rivers (Williams et al., 2009). The collection of effects data can cover any effect, at any level of organisation, on any organism. Most, and possibly all, of that effect data are likely to come from laboratory studies. The median environmental (river) concentration and the median effect concentration are determined from all of the individual data points. The smaller the difference between

the two median values, the greater the degree of concern. An example of this approach is provided in figure 1; it is taken from Donnachie et al., 2015.

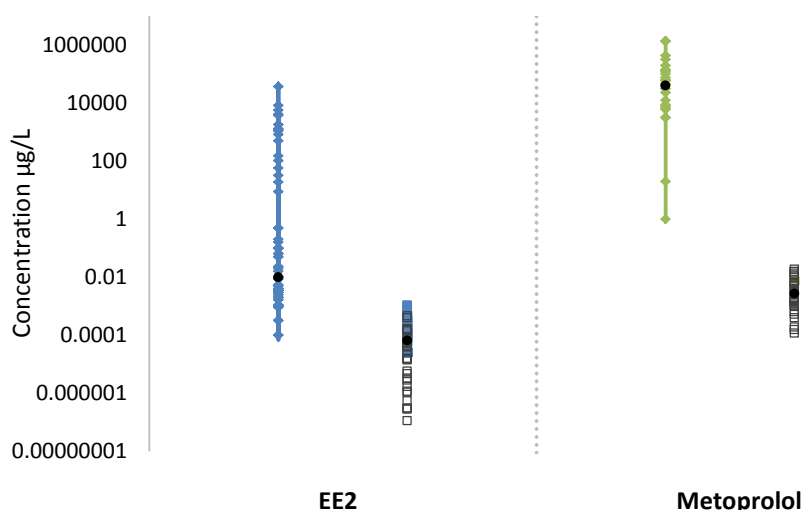


Figure 1: Comparison of the effect concentrations (left-hand column of each pair) and river concentrations (right-hand column) of two human pharmaceuticals: the synthetic oestrogen ethinyl oestradiol (EE2) and the beta-blocker metoprolol. The median values are plotted as black circles.

Note that the two median values for EE2 are only about 10-fold apart, and that there is some overlap between the river concentrations and the effect concentrations: this suggests a potential concern. In contrast, the data for metoprolol would suggest that river concentrations are orders of magnitude below any likely effect concentration.

Completing this initial step is, of course, possible only if appropriate data are available in the literature. Currently this is the case for only about 30 (of the 3000) pharmaceuticals in everyday use, albeit those 30 are considered likely to include some of those of most concern. For all other pharmaceuticals, we suggest starting at Step 2.

Step 2: The read-across approach

The read-across hypothesis states that pharmaceuticals will have effects on non-target species (e.g. fish) if plasma concentrations in those species reach human therapeutic concentrations. Further, the hypothesis states that the effects will be essentially the same in the non-target species as they are in humans; this assumption is based on the high degree of conservation of drug targets throughout the vertebrates at least. Simple models can be used to predict what plasma concentration in fish would likely be reached at any particular river concentration. These models seem to be quite accurate (see, for example, Margiotta-Casaluci et al., 2015). The models can also be used in reverse, to predict what river concentration of a pharmaceutical would be required to produce a plasma concentration in fish likely to cause effects.

Currently the read-across approach is only applicable to potential effects on aquatic vertebrates. Although the hypothesis is now well established for fish more research is required to know if a similar approach could be utilized to predict effects (or support those reported) on invertebrates, or even algae. As with step 1, an attraction of this approach is that it allows relative assessments of pharmaceuticals and limits bias. Another attraction is that it can be applied to any pharmaceutical, and it is relatively quick and easy to do.

Step 3: Assess the concern of a pharmaceutical based upon a range of factors

These factors should, as a minimum, cover the amount of the pharmaceutical used, its mode of action, metabolism in patients, degree of degradation in the environment, and degree of uptake into biota. The objective would be to make an informed judgement on whether or not the pharmaceutical was likely to be present and persistent in the aquatic environment in an active form, as parent molecule or transformation product (Liu & William, 2007); whether or not it was likely to be taken up by, and bioconcentrate in, biota, and if so in what groups; and whether or not the concentration in the biota would be high enough to cause an effect, and if so, how adverse that effect would be. The purpose of this step is to refine the environmental risk assessment.

The factors that could be considered in this intelligent approach are outlined in Table 1. It would be possible to employ a points system, with the most important factors being given more points than the factors considered less important.

In theory, Step 3 is applicable to just about any pharmaceutical, old as well as those newly on the market, and for which little, if any, environmental occurrence or effects data exist. Based on the factors indicated in Table 1, it should be possible to quickly make a preliminary judgement on whether or not a pharmaceutical lacking much environmental data could conceivably present a hazard to the environment. Step 3 can be refined to give greater confidence in the conclusion reached by utilizing the read-across approach (as described in Step 2).

Table 1: Data requirements of the principal methods

Number	Data requirement	Step 1 Concentration proximity approach	Step 2 Read across approach	Step 3* Intelligent approach
1	Drug consumption data	Usable	Not needed if 5 and 6 exist	Desirable
2	LogD for drug	Not needed	Vital	Desirable
3	Human plasma therapeutic dose	Not needed	Vital	Not needed
4	% excreted by patient	Usable	Not needed if 5 and 6 exist	Desirable
5	% removed in sewage treatment	Usable	Not needed if 5 and 6 exist	Desirable
6	Measured sewage effluent concentrations	Usable	Usable	Usable
7	Measured river water concentrations	Vital if no modelled data	Usable	Step assumes these measurements don't exist
8	Modelled river water concentrations	Vital if no measured data	Vital	Helpful
9	River water removal rate	Not needed	Not needed	Desirable
10	Knowledge of mode of action	Not needed	Not needed	Desirable
11	Predicted fish internal concentration	Not needed	Would be an outcome of the model	Desirable
12	Predicted algae and invertebrate internal concentration	Not needed	Not needed	Desirable
13	Knowledge of presence/absence of receptors in different biota	Not needed	Not needed	Desirable
14	Calculated bioconcentration factor	Not needed	Outcome of the model	Desirable
15	Ecotoxicity data for aquatic biota	Vital	Not needed	Step assumes this data does not exist

* Note: It would be possible to apply a points system to these indicators to arrive at threshold values indicating levels of concern

Step 4: Assessing difficult cases with the use of expert opinion

There are likely to be certain pharmaceuticals, and certain effects, that cannot adequately be assessed using the steps summarized above. One example is the possibility that antibiotics present in the environment could lead to the development of antibiotic resistance in microbes (particularly viruses and bacteria) in those environments, and that the genes conferring that resistance could transfer to human pathogens. Another might be the nano-pharmaceuticals now being increasingly utilised: assessing the environmental impact of these with any confidence is currently very difficult.

There may be occasions where an assessment is required where both information and time are very limited. This is where 'expert judgement' may have to be used based on prior knowledge from other similar compounds. However, this should not be overplayed as our knowledge is still limited. We should take particular interest in pharmaceuticals which are known to be hormonal agonists or antagonists. By their very nature hormones can stimulate a whole cascade of effects at very low

concentrations. Antibiotics are designed to inhibit prokaryotes and so effects on cyanobacteria in the environment would be a potential impact.

Situations such as these will have to be dealt with on a case-by-case basis. It is possible that the conclusion could be that until further evidence becomes available, the degree of concern cannot be determined.

HSAC use of the Steps approach

The steps summarised in Table 2 broadly represent a hierarchy of i) scientific (and other) evidence supporting HSAC's opinion and ii) varying level of confidence due to the quality of evidence available at each of the individual steps of the procedure which will be reported when HSAC delivers its opinion. Figure 2 indicates the workflow that HSAC will adopt when providing an opinion on a provisional PoC.

Table 2: Overview of the HSAC approach for PoCs

Approach	Outcome
STEP 1 (Concentration proximity approach)	Based on knowledge of water concentrations and ecotox effect concentration. Allows pharmaceuticals to be judged against each other and also against other chemicals. In theory unbiased and repeatable.
STEP 2 (Read across approach)	Based on assumption that pharmaceutical plasma concentration in fish is key to whether effects will happen in the environment. Results can be judged against other drugs. In theory unbiased and repeatable.
STEP 3 (Intelligent approach)	Takes all available drug property, fate and biological data to review its potential hazard.
STEP 4 (Expert opinion approach)	Of possible value if prior knowledge on the type of drug and its class are known.

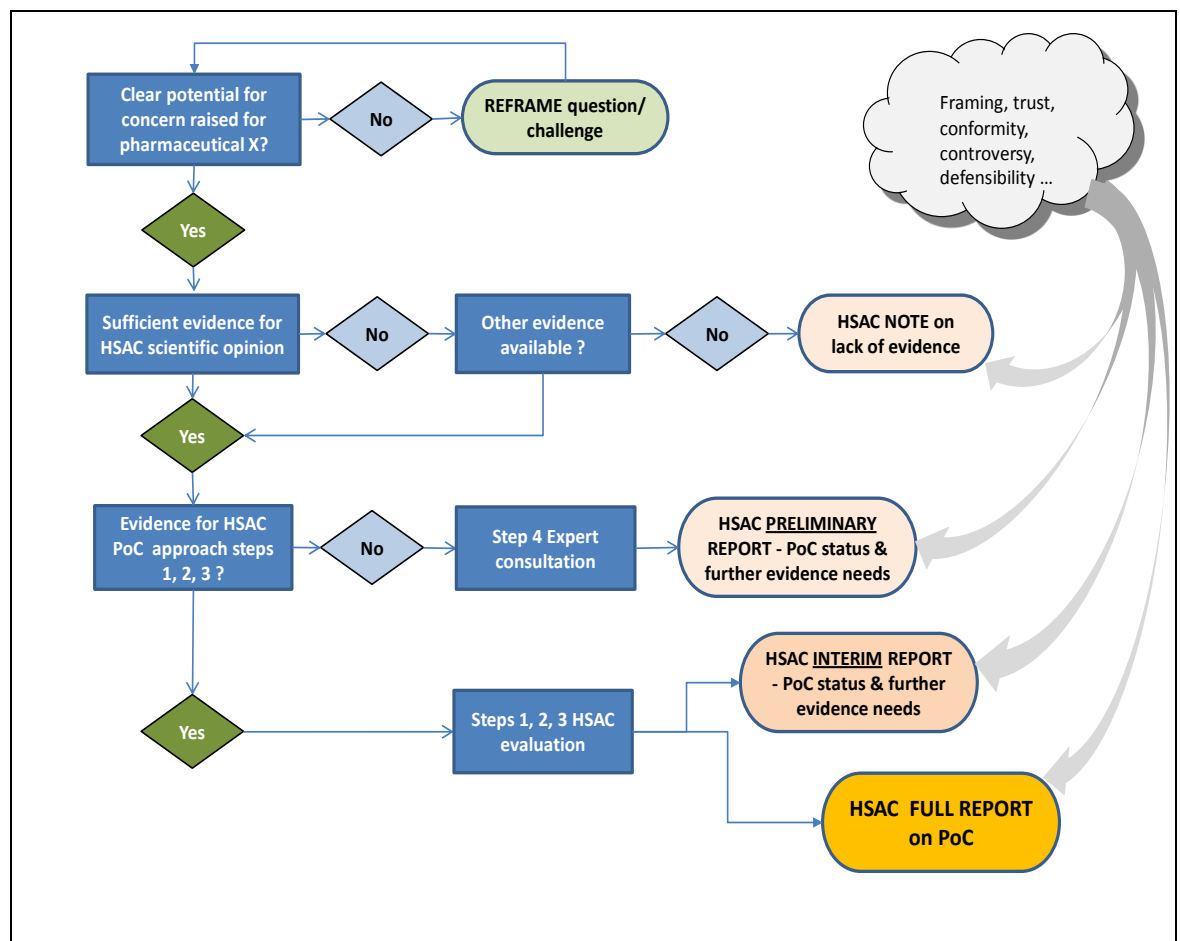


Figure 2: Workflow of HSAC approach

Note on the terrestrial environment

The strategy described above is focussed on the aquatic environment which is the one most likely to be adversely affected by human pharmaceuticals. Contamination of the terrestrial environment by human pharmaceuticals could occur when sludge from wastewater treatment works is applied to land. Extremely little is known about this route of exposure, and hence any quantification of the potential hazard is not possible presently. But it is possible to make some general points: firstly, sludge applications are not uniform across the land or even agricultural land and their use in food crops is restricted; secondly, the opportunity for sorption and biodegradation is much higher than in rivers; thirdly, the organisms most directly exposed are not vertebrates, so many of the drug target sites probably won't exist. This situation is different for veterinary pharmaceuticals, where considerably more is known about their potential effects on the terrestrial environment.

References

- Donnachie, R.L., Johnson, A.C. and Sumpter, J.P. 2015. A rational approach to selecting and ranking some pharmaceuticals of concern for the aquatic environment and their relative importance compared to other chemicals. *Environmental Toxicology and Chemistry*, in press.
- Liu, Q.-T. and William, H.E. 2007. Kinetics and degradation products for direct photolysis of β blockers in water. *Environmental Science and Technology*, 41, 803-810.
- Margiotta-Casaluci, L., Owen, S.F., Cummings, R.I., de Polo, A., Winter, M.J., Panter, G.H., Rand-Weaver, M. and Sumpter, J.P. 2014. Quantitative cross-species extrapolation between humans and fish: the case of the anti-depressant fluoxetine. *PLOS ONE* 9, e110467.
- Williams R.J., Keller V.D.J., Johnson A.C., Young A.R., Holmes M.G.R., Wells C., et al. A National Risk Assessment for Intersex in Fish Arising from Steroid Estrogens. *Environmental Toxicology and Chemistry* 2009; 28: 220-230.
-