Department for Environment, Food and Rural Affairs

Hazardous Substances Advisory Committee

Working paper – how would HSAC characterize a pharmaceutical of concern regarding risks in the environment?

February 2016

Scope

This document is designed as guidance for the Hazardous Substances Advisory Committee (HSAC) when 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. It is noted that, in general, the majority of active pharmaceutical ingredients (APIs) are considered to have an insignificant environmental risk (environmental risk assessments according to current methods typically have safety factors >100 fold). Veterinary medicines are not within the scope of this document nor is antimicrobial resistance (HSAC recognises that this issue is under consideration 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, clearly, 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 (it is applicable also to the general aquatic environment).

This document is consistent with the principles of the HSAC paper "*Considering Evidence: the approach taken by the Hazadous Substances Advisory Committee in the UK*" (HSAC, 2015). The use of a given human pharmaceutical 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 licensed for use in any one country (e.g. Kinch et al., 2014). Relative to many industrial chemicals, the amounts used are small, nevertheless more than a tonne 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 or degraded 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, while others present strong evidence to the contrary. A very recent example concerns metformin (a very widely prescribed anti-diabetic drug):

Niemuth, N.J. and Klapper, R.D. 2015. Emerging wastewater contaminant metformin causes intersex and reduced fecundity in fish. Chemosphere 135, 38-45.

Moermond,C.T.A and Smit, C.T. 2015. Derivation of Water Quality Standards for carbamazepine, 39 metoprolol and metformin and comparison with monitoring data. Environ Toxicol Chem., Accepted 40 Article DOI: 10.1002/etc.3178

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 guidance 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 existing literature to provide a first indication of the possible degree of concern

Here we assume the compound has been on the market for several years and a certain amount of relevant research has been carried out. In this step, information from the scientific literature is collected and assessed (if available) on both the measured 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 and to include deliberately all openly-available reports. It should be noted that this approach differs from more regulatory-focussed proceedures and/or meta-analyses where reliability and relevance checks are commonly conducted prior to inclusion of results for individual studies. With pharmaceuticals there are often few studies in the literature, so an approach that starts out as too prescriptive may leave little published information left to carry out a worthwhile analysis. 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 Fig 1; it is taken from Donnachie et al., 2015.

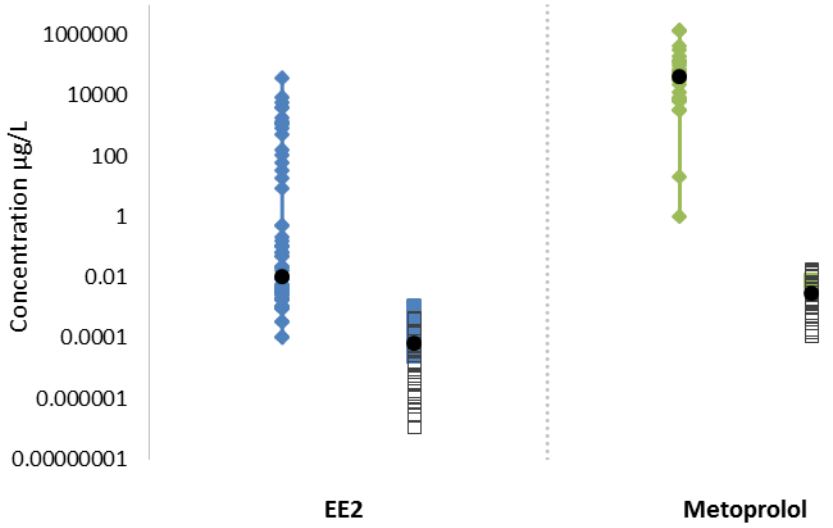

Figure 1: Comparison of the effect concentrations (left-hand data of each pair) and river concentrations (right-hand column) of two human pharmaceuticals: the synthetic oestrogen ethinyl oestradiol (EE2) and the beta-blocker metoprolol. The median values are plotted as black circles.

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. Only where there is close proximity between effect and measured river concentrations is further analysis of the 'quality' of the ecotoxicity data warranted.

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.

[HSAC recognises that this step is structured to be based on literature-published values. We also recognise that industry is likely to possess relevant data that it provides to national environmental regulators etc. When asked for an opinion on a possible PoC, HSAC will consult sources such as company webpages, data repositories etc., and will request input from industry for access to relevant studies and data in addition to using published studies.]

STEP 2: The read-across approach

With step 2 we assume that measured water concentrations and ecotoxicity data are absent, such as might be the case with a pharmaceutical which is new to the market. 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 (in plasma). 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. Essentially, the more the pharmaceutical has lipophilic characteristics the higher the plasma concentration with respect to the external water concentration would be predicted. These models seem to be quite accurate (see, for example, Margiotta-Casaluci et al., 2014). 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 utilised 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 consumption, fate and presence of receptors

For Step 3 we also assume that measured water concentrations and ecotoxicity data are absent, but unlike Step 2, a range of factors are now considered. 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 and metabolism/elimination from 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 might be.

A comparison of the information needed to assess whether a pharmaceutical in the environment is of concern is 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. Step 3 may be able to give greater confidence in the conclusion reached by utilising 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 6 and 7 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 6 and 7 exist	Desirable
5	**% removed in sewage treatment**	Usable	Not needed if 6 and 7 exists	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 summarised above. One potential example, which HSAC has recognised, is 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.

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, regulatory 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 Pharmaceuticals of concern

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 risk.
STEP 4 (Expert opinion approach)	Of possible value if prior knowledge on the type of drug and its class are known.

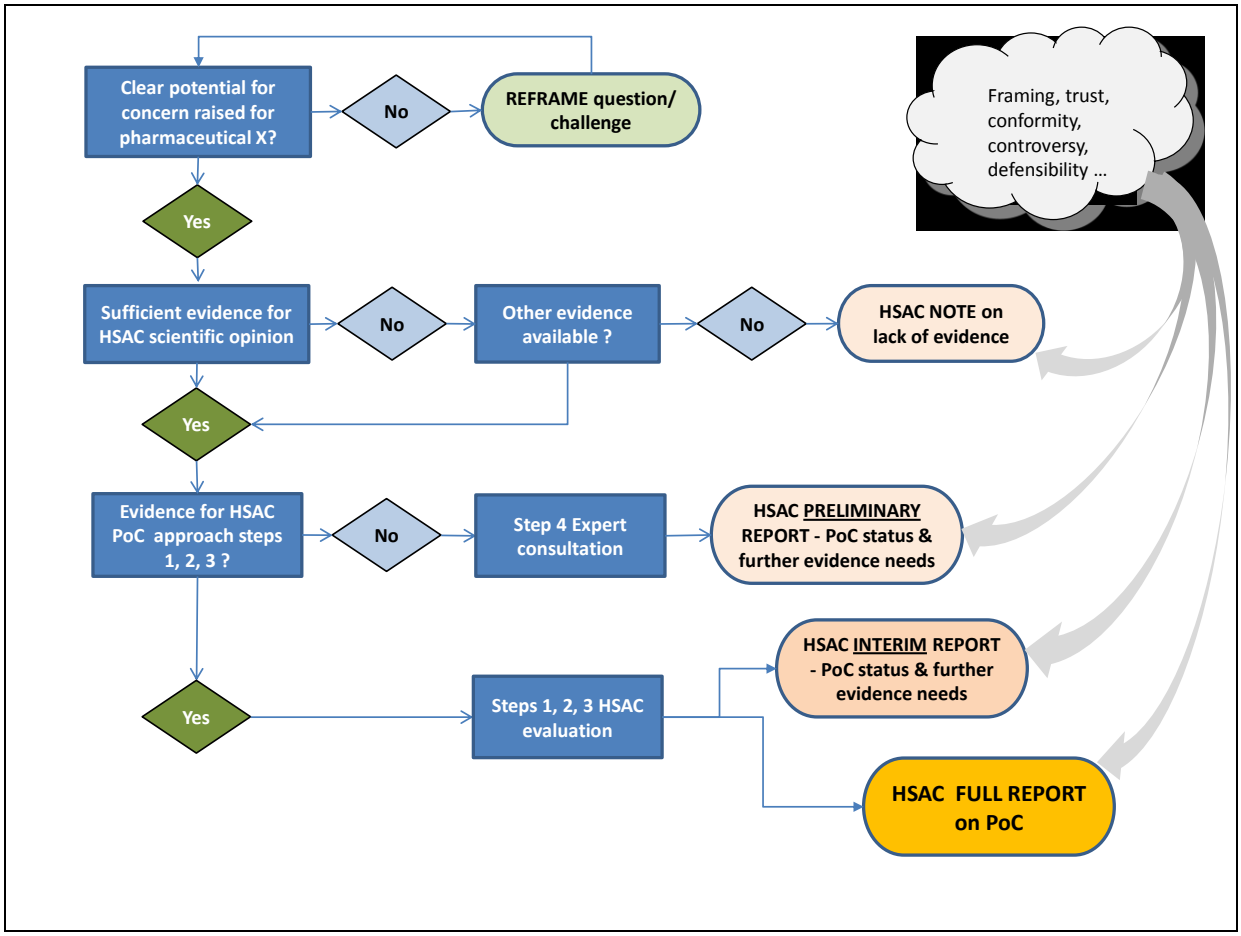

Figure 2: Workflow of HSAC approach

This paper has focussed on the use of the HSAC procedure as a means of identifying a level of concern that can be expressed over the presence of an individual human pharmaceutical in the environment. In reporting the results of applying this procedure and the principles of the HSAC paper "Considering Evidence: the approach taken by the Hazadous Substances Advisory Committee in the UK" to a given case HSAC will provide an opinion that is:

i. Based on available evidence

ii. Transparent

iii. Expresses the HSAC opinion over the level of concern in terms such as 'High degree of concern – immediate action to reduce discharge to the environment is recommended; Low degree of concern – no further action recomended'. The narrative of the opinion will make clear grounds on which the HSAC's level of concern is based.

In review of this document by a number of organisations and HSAC it has been recognised that the approach outlined for pharmaceuticals of concern can be applied to any substance in the environment over which concern may exist and HSAC will make use of this procedure when examining such cases where appropriate.

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 risk 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 (Kools et al., 2008).

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.

HSAC (2015). Considering evidence: The approach taken by the Hazardous Substances Advisory Committee in the UK. Hazardous Substances Advisory Committee, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/452336/considering-evidence-hsac-approach.pdf, accessed 9 February 2016.

Kinch, M.S., Patridge, E., Haynesworth, A., Kinch, S.J. and Hoyer, D., (2014). An overview of FDA-approved new molecular entities: 1827–2013. Drug Discovery Today 18 (9), 1033-1039.

Kools S.A.E., Boxall A.B.A., Moltmann J.F., Bryning G., Koschorreck J., II, Knacker T.(2008). A Ranking of European Veterinary Medicines Based on Environmental Risks. Integrated Environmental Assessment and Management 4: 399-408.

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. (2009). A National Risk Assessment for Intersex in Fish Arising from Steroid Estrogens. Environmental Toxicology and Chemistry 28: 220-230.