Scientific Committee on Health and Environmental Risks

SCHER

OPINION ON

"CHEMICALS AND THE WATER FRAMEWORK DIRECTIVE: DRAFT ENVIRONMENTAL QUALITY STANDARDS"

Ethinylestradiol (EE2)

SCHER adopted this opinion at its 12th plenary on 30 March 2011

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHER

Opinions on risks related to pollutants in the environmental media and other biological and physical factors or changing physical conditions which may have a negative impact on health and the environment, for example in relation to air quality, waters, waste and soils, as well as on life cycle environmental assessment. It shall also address health and safety issues related to the toxicity and eco-toxicity of biocides.

It may also address questions relating to examination of the toxicity and eco-toxicity of chemical, biochemical and biological compounds whose use may have harmful consequences for human health and the environment. In addition, the Committee will address questions relating to methodological aspect of the assessment of health and environmental risks of chemicals, including mixtures of chemicals, as necessary for providing sound and consistent advice in its own areas of competence as well as in order to contribute to the relevant issues in close cooperation with other European agencies.

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1. BACKGROUND

Article 16 of the Water Framework Directive (WFD, 2000/60/EC) requires the Commission to identify priority substances among those presenting significant risk to or via the aquatic environment, and to set EU Environmental Quality Standards (EQSs) for those substances in water, sediment and/or biota. In 2001 a first list of 33 priority substances was adopted (Decision 2455/2001) and in 2008 the EQSs for those substances were established (Directive 2008/105/EC or EQS Directive, EQSD). The WFD Article 16 requires the Commission to review periodically the list of priority substances. Article 8 of the EQSD requires the Commission to finalise its next review by January 2011, accompanying its conclusion, where appropriate, with proposals to identify new priority substances and to set EQSs for them in water, sediment and/or biota. The Commission is now aiming to present its proposals to Council and the Parliament by June 2011.

The Commission has been working on the abovementioned review since 2006, with the support of the Working Group E (WG E) on Priority Substances under the Water Framework Directive Common Implementation Strategy. The WG E is chaired by DG Environment and consists of experts from Member States, EFTA countries, candidate countries and more than 25 European umbrella organisations representing a wide range of interests (industry, agriculture, water, environment, etc.). A shortlist of 19 possible new priority substances was identified in June 2010. Experts nominated by WG E Members (and operating as the Sub-Group on Review of Priority Substances) have been deriving EQS for these substances and have produced draft EQS for most of them. In some cases, a consensus has been reached, but in some others there is disagreement about one or other component of the draft dossier. Revised EQS for a number of existing priority substances are currently also being finalised.

The EQS derivation has been carried out in accordance with the draft Technical Guidance on EQS reviewed recently by the SCHER. DG Environment and the rapporteurs of the Expert Group that developed the TGD have been considering the SCHER Opinion and a response is provided separately.

2. TERMS OF REFERENCE

2.1 General requests to SCHER

DG Environment now seeks the opinion of the SCHER on the draft EQS for the proposed priority substances and the revised EQS for a number of existing priority substances. The SCHER is asked to provide an opinion for each substance. We ask that the SCHER focus on:

1. **whether the EQS have been correctly and appropriately derived, in the light of the available information[1] and the TGD-EQS;**

2. **whether the most critical EQS (in terms of impact on environment/ health) has been correctly identified.**

[1] The SCHER is asked to base its opinion on the technical dossier and the accompanying documents presented by DG Environment, on the assumption that the dossier is sufficiently complete and the data cited therein are correct.

Where there is disagreement between experts of WG E or there are other unresolved issues, we ask that the SCHER consider **additional points**.

2.2 Specific requests on Ethinylestradiol (EE2)

The SCHER is asked to consider the two generic questions in the request as well as the following specific point.

The pharmaceutical industry experts in the Sub-Group have derived an alternative EQS for EE2 which is presented in the attached journal manuscript. An earlier draft of the manuscript was provided to the dossier lead in September 2010 and taken into consideration in the main EE2 dossier. The industry experts remain supportive of their own derivation, which leads to an EQS of 0.1 ng/l instead of 0.035 ng/l. The SCHER is asked to consider whether the derivation in the main EQS dossier is appropriate or whether the industry approach should be taken further into consideration.

3. OPINION

3.1. Responses to the general requests

1. whether the EQS have been correctly and appropriately derived, in the light of the available information and the TGD-EQS;

17α-ethinylestradiol (EE2) is a potent synthetic steroid and the dossier adequately indentifies the endocrine disrupting properties of EE2 as the key mechanism of action for the derivation of the EQS. The key relevance of this mechanism of action for addressing the adverse effects of EE2 on aquatic ecosystems is confirmed through the comparison of the endpoints associated and non-associated to endocrine disruption. Therefore, some of the generic assumptions presented in the TGD-EQS need to be adapted for addressing properly the specificities of such a chemical.

The SCHER considers that in the derivation of the EQS of EE2 for the pelagic freshwater community the available information has been properly considered. Instead of following strictly the recommendations of the TGD-EQS the proposal generally presents a scientifically sound analysis justifying the deviations from the guidance.

In considering the toxicity data for EE2 both the reliability and the ecological relevance of the endpoints and taxonomic groups have been taken into account. Acute effects have been considered of no relevance and therefore no MAC-EQS has been derived. Enpoints related to vitellogenin production and similar observations were considered of insufficient ecological relevance, and, therefore, were not taken into account for the derivation of the QS for EE2. The assessment focused on endpoints with the potential to affect population sustainability, e.g. reproductive output, hatching, fertilisation success. This approach is supported by the SCHER. However, it should be noted that the SCHER cannot comment on the specific selection of the NOECs used for each species as the descriptions provided in the dossier are in most cases generic and do not allow an individual assessment. For example, the lowest value on *Oryzias latipes* from Balch et al. (2004) is reported as $NOEC_{reproduction}$ = 0.2ng/l, and therefore should in principle be considered as ecologically relevant, but has been excluded from the Species Sensitivity Distribution (SSD) without explanation.

The sensitivity of the different taxonomic groups was addressed and instead of a SSD based on all available information the QS has been derived using exclusively the chronic toxicity studies on fish and amphibians. Non standardised assays, targeted to the identified mechanism of action have been considered relevant and as the test design and testing conditions differ among the studies available for the same species, the SSD has been based on the most sensitive ecologically relevant endpoint for each species instead of using the geometric mean of the available NOECs.

The SCHER supports this approach and considers that the HC5 from the SSD distribution of 0.07 ng/l should be the basis for the derivation of the AA-QS for the pelagic community.

Regarding the need for an assessment factor higher than 1, the SCHER considers that the arguments related to molluscs and amphibians are not sufficiently convincing for a chemical with a large set of valid studies specifically designed for addressing the well identified mechanism of action. As a principle, the SCHER considers that the HC5 obtained from the SSD of the most sensitive taxonomic group if based on good quality data should be sufficient for avoiding the need for an assessment factor, as recognised in the TGD-EQS. However, the Committee considers that in this particular case, there are additional reasons that indicate a significant remaining uncertainty. The results on the Chinese rare minnow are partially used in the dossier as supporting argument for the assessment factor of 2. After assessing the results published by Zha et al. (2007, 2008a, 2008b), SCHER considers that not only the sensitivity of this species but also the increase in toxicity observed among generations should be taken into account. The concern for effects only appearing after repeated long term exposure is confirmed by the results from a whole-lake experiment showing near extinction of fathead minnow from the lake in the second year of treatment (Kidd et al., 2007) at seasonal concentrations just 5 times higher that the full life-cycle NOEC reported for the same species (Länge et al., 2001). It should be noted that most NOECs used in the SSDs do not correspond to multigeneration studies. The database indicates large differences in sensitivity among species for the same reproductive endpoint and within the same species for different endpoints. The differences can be related to the very specific but complex mechanism of action of EE2 in fish, which affect the expression of a variety of genes, which differ between sexes and among tissues (e.g. Filby et al., 2007). Therefore, the endpoints included in the SSD may not necessarily be the most sensitive relevant parameter for each species. These uncertainties justify the use of an assessment factor higher than 1.

As a consequence, the SCHER supports the proposed AA-$QS_{freshwater,eco}$ of 0.035ng/l.

Unfortunately, the derivation of the other QS has not considered the available information on the mechanism of action. Instead, the TGD-EQS recommendations have been strictly followed without assessing if these generic guidelines are or not applicable to this specific substance.

An additional assessment factor of 10 was applied to the proposed AA-$QS_{freshwater}$ to estimate the AA-$QS_{saltwater}$. This approach is inconsistent with the use of an SSD based exclusively on fish and amphibians as the most sensitive taxa, which includes freshwater and marine species on the basis of no observed differences between the freshwater and saltwater data sets.

The direct extrapolation of a the AA- $QS_{freshwater,eco}$ value based on the sensitivity for fish and amphibians for the derivation of the QS for sediment using the equilibrium partitioning method does not consider the limited relevance of these groups for assessing effects on benthic organisms exposed via contaminated sediment.

Regarding the assessment of secondary poisoning, the QS is based on the NOAEL of 0.1µg/kg/day for male rats reported in the study by Latendresse et al (2009), but the selected endpoint is not indicated, and therefore its ecological relevance cannot be verified. In addition the standard assessment factors are used despite the fact that this is a several-generations study, with exposure up to F3 followed by observations in the unexposed generations F4 and F5. The AFs for secondary poisoning recommended in the TGD-EQS depend on the study duration in addition to interspecies variation. Taking into account that the mechanism of action is known and that instead of a standard chronic NOEC a several generations study is available, a specific justification for the proposed AF should be provided.

Regarding human health-related endpoints, the opinion lists a variety of studies investigating different endpoints. Selection of studies for deriving quality standards should be based on relevance of the route of administration to the actual pathway of exposure (oral) and the endpoints determined. Therefore, studies with subcutaneous injection are of little relevance. Moreover, some recent studies are missing (US National Toxicology Program, Toxicology and carcinogenesis study of ethinyl estradiol (feed study); Multigenerational Reproductive Toxicology study of ethinyl estradiol; Mathews et al. Toxicol Sci 112, 331-43, 2009; Howdeshell et al., Toxicol. Sci 102, 371-82, 2008). The results of these studies need to be integrated in the assessment. It needs to be questioned if the general extrapolation approach based on animal species with a higher sensitivity as compared to humans (e.g. Witorsch, Food Chem. Tox. 40, 905-12, 2002) is scientifically justified.

The formal approach to derive EQS for human health and secondary poisoning follows the TGD.

2. whether the most critical EQS (in terms of impact on environment/health) has been correctly identified.

The SCHER considers that the most critical EQS in terms of impact on environment/health has been correctly identified.

3.2. Responses to the specific requests on Ethinylestradiol (EE2)

The derivation of PNEC in the scientific manuscript presented by industry is scientifically sound and transparent. Despite the conceptual differences between a PNEC and an EQS identified by the Committee in a previous opinion (SCHER, 2010), the SSD distribution presented by industry follows the same conceptual approach as the one applied by the dossier and offers a proper basis for developing the EQS.

In fact, the SCHER notes that although the selection of the data is not exactly the same, the outcome, in terms of the HC5 is similar to that proposed in the dossier. The different alternatives presented in the sensitivity analysis demonstrate that the data fit the lognormal model and the HC5 falls in a fairly constant range, from 0.06 to 0.08 ng/l; when two studies of less than 40 days duration (with higher NOECs) are removed from the dataset and a Chinese rare minnow NOEC of 0.1 ng/L is used, the HC5 is exactly 0.07 ng/L, which is the HC5 proposed in the dossier.

Therefore, the approach presented by industry is not contradictory and in fact supports the proposal of an HC5 of 0.07 ng/L.

The difference is that based in this approach, the industry paper suggests a PNEC of 0.1 ng/L, that means an assessment factor lower than 1, while the dossier proposes an assessment factor of 2.

For the reasons expressed above, the SCHER considers that an assessment factor higher than 1, as proposed in the dossier, is appropriate in this case and, as already indicated, supports the proposed AA-$QS_{freshwater,eco}$ of 0.035ng/l.

4. LIST OF ABBREVIATIONS

AA-QS	annual average quality standard
DAR	draft assessment report
DT50	half life for degradation or dissipation
EQS	environmental quality standard
HC5	hazardous concentration for 5% of the species
MAC-QS	maximum allowable concentration quality standard
PEC	Predicted Environmental Concentration
PBT	Persistent, Bioaccumulative and Toxic
SSD	species sensitivity distribution
TGD-EQS	Technical Guidance Document - Environmental Quality Standards
WFD	Water Framework Directive

5. REFERENCES

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