Scientific Committee on Health and Environmental Risks

SCHER

OPINION ON

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

17β-estradiol (E2)

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

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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 β-estradiol (E2)

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

(i) The dossier calculation of the EQS takes into account a **study by Lahnsteiner et al** (2006). Inclusion of the study changes the EQS from 0.53 to 0.4 ng/l (a combination of greater sensitivity, i.e. lower NOEC, but increased certainty, i.e. lower AF). Pharmaceutical industry experts in the sub-group do not consider the inclusion of this study to be appropriate. The attached document explains their position. On the other hand, the study has been accepted by external reviewers of the Swiss national standard for E2; their review could be provided to SCHER if potentially helpful. The dossier lead and another Member State also considered it appropriate to include. The SCHER is asked to consider whether the main E2 EQS dossier takes appropriate account of the Lahnsteiner et al study.

(ii) The pharmaceutical industry experts in the Sub-Group have derived an alternative EQS for E2 which is presented in the attached journal manuscript (same as for EE2, see above). An earlier draft of the manuscript was provided to the dossier lead in September 2010 and taken into consideration in the main E2 dossier. The industry experts remain supportive of their own derivation, which leads to an EQS of 2.0 ng/l instead of 0.4 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.

(iii) The relative (endocrine disruptive) potency of E2 and EE2 has been given some consideration. An analysis by the Swiss agency could be provided to the SCHER; the agency concluded that EE2 was roughly 10 times more potent than E2. The SCHER is asked to consider relative potency in coming to its conclusions regarding the appropriateness of the EQSs derived for the two substances.

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;

17 β-estradiol (E2) is a natural estrogen and the dossier adequately indentifies the endocrine disrupting properties 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 E2 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 E2 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 E2 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. Vitellogenin production endpoints and similar observations were considered of insufficient ecological relevance and not considered as relevant endpoints for the derivation of the QS for E2; focusing the assessment on endpoints with the potential to affect population sustainability, e.g. reproductive output, hatching, fertilisation success. However, it should be noted that 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 very generic and insufficient for a peer-review assessment. For example, the selected NOEC for *Danio rerio* is 25 ng/l while the study from Nash et al. (2004) reports relevant effects at lower concentrations, $NOEC_{reduced\ egg\ survival}$ <5ng/l and the study is considered of good quality.

The sensitivity of the different taxonomic groups was addressed and instead of a Species Sensitivity Distribution (SSD) based on all available information the QS has been derived using exclusively the chronic toxicity studies on fish. The data on amphibians showed low sensitivity and have not been considered in the SSD for E2 although amphibian data were included in the SSD presented for EE2. 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 0.8 ng/l should be the basis for the derivation of the AA-QS for the pelagic community, although it notes that the overall level of information is lower than that supporting the HC5 for EE2. The dossier recognises this fact and suggests the comparison of the estrogenic potency of both estrogens for supporting the QS derivation. The dossier concludes that the in vivo potency of EE2 is probably about ten times higher than that of E2, but a full analysis is not presented; the request to SCHER offers an additional assessment supporting this potency comparison. The SCHER considers that the comparison of both SSDs clearly supports the assessment of an order of magnitude difference between the potency of both estrogens and, therefore, has not considered it necessary to request the additional supporting document.

Regarding the need for an assessment factor of 2, the SCHER notes that the arguments related to molluscs and amphibians, used for EE2, have not been used for E2. The evidence available for E2 is not as abundant as for EE2, however, as both substances share common mechanisms of action, the general arguments presented in the SCHER opinion for EE2 (SCHER, 2011) are also applicable to E2. It should be noted that some NOECs used in the SSDs correspond to short exposure periods.

The dossier considers the inclusion in the SSD of the NOEC from a study by Lahnsteiner et al (2006), which was lower than the other reported NOECs by a factor of 10 fold, as an argument for justifying that an assessment factor larger than 2 is not required. The SCHER considers that this is a valid argument. The potency comparison between E2 and EE2 also supports the factor of 2 as this leads to an order of magnitude difference for the QS as well as for the HC5.

As a consequence, the SCHER supports the proposed $AA\text{-}QS_{freshwater,eco}$ of 0.4 ng/l.

As for EE2, 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 are 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 on fish, 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 the AA- $QS_{freshwater,eco}$ value based on the sensitivity for fish for the derivation of the QS for sediment using the equilibrium partitioning method does not consider the limited relevance of this taxonomic group for assessing effects on benthic organisms exposed via contaminated sediment.

Regarding the assessment of secondary poisoning, the argument that there is uncertainty in the potential for bioaccumulation as the measured whole body BCF value is low in contrast to the log Kow is not supported by the SCHER. The Committee considers that, when available, valid BCFs should be used instead of the Kow, and that this low potential for accumulation is confirmed by the supporting studies. Therefore the SCHER considers that the trigger for developing $QS_{biota,secpois}$ is not met.

Regarding human health-related endpoints, the opinion lists a variety of studies, some only available as abstracts. 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 in an animal model with claimed high sensitivity to estrogens (CD-1 mouse) are missing (Tyl et al., Reprod. Toxicol. 25, 144-60, 2008; Tyl et al., Toxicol Sci 102, 392-412, 2008). These studies report NOAELs of approximately 1 microg/kg bw/day after dietary administration and should be used as a basis for the assessment.

Despite the likely thresholded mode-of-action for carcinogenicity of E2, LOAELs or NOAELs regarding carcinogenicity should not be use in a risk assessment context.
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 β-estradiol (E2)

(i) The dossier calculation of the EQS takes into account a **study by Lahnsteiner et al** (2006). Inclusion of the study changes the EQS from 0.53 to 0.4 ng/l (a combination of greater sensitivity, i.e. lower NOEC, but increased certainty, i.e. lower AF). Pharmaceutical industry experts in the sub-group do not consider the inclusion of this study to be appropriate. The attached document explains their position. On the other hand, the study has been accepted by external reviewers of the Swiss national standard for E2; their review could be provided to SCHER if potentially helpful. The dossier

lead and another Member State also considered it appropriate to include. The SCHER is asked to consider whether the main E2 EQS dossier takes appropriate account of the Lahnsteiner et al study.

As the mechanism of action of natural estrogens such as E2 is self-evident, most reprotoxicity studies have been conducted using specifically designed protocols, conditions and selection of endpoints. This is well justified by the mechanism of action as indicated above. The Lahnsteiner et al. study clearly indicates that at ≥1.0 ng/l a severe reduction of reproductive capacity must be expected due to the combined negative effect on semen volume, sperm density, sperm motility and sperm fertility. These effects should be considered ecologically relevant.
Consequently, the SCHER cannot support the industry arguments for excluding this specific study and considers that the inclusion of the Lahnsteiner et al. study in the SDD is appropriate.

(ii) The pharmaceutical industry experts in the Sub-Group have derived an alternative EQS for E2 which is presented in the attached journal manuscript (same as for EE2, see above). An earlier draft of the manuscript was provided to the dossier lead in September 2010 and taken into consideration in the main E2 dossier. The industry experts remain supportive of their own derivation, which leads to an EQS of 2.0 ng/l instead of 0.4 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.

The industry approach is similar to that presented in the dossier but has some differences regarding the actual data included in the SSD. The sensitivity analysis included in the industry paper confirms the relevance of the inclusion of NOEC values below 1 ng/l. As the SCHER considers that the inclusion of the Lahnsteiner et al study in the SSD is appropriate, and this study has not been included in the industry SSD, the SCHER considers that the derivation presented in the dossier is more appropriate.

(iii) The relative (endocrine disruptive) potency of E2 and EE2 has been given some consideration. An analysis by the Swiss agency could be provided to the SCHER; the agency concluded that EE2 was roughly 10 times more potent than E2. The SCHER is asked to consider relative potency in coming to its conclusions regarding the appropriateness of the EQSs derived for the two substances.

As E2 and EE2 share the same mechanisms of action a potency consideration is relevant as supporting evidence. Based on the comparison of the SSDs, the SCHER agrees with the estimation of EE2 as roughly 10 times more potent than E2 for fish in vivo. The Committee considers that the potency assessment provides additional support to the EQSs proposed in the dossiers for both substances.

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

Lahnsteiner F, Berger B, Kletzl M, Weismann T (2006): Effect of 17β-estradiol on gamete quality and maturation in two salmonid species. Aquatic Toxicology. 79:124–131.

SCHER (Scientific Committee on Health and Environmental Risks) (2010), Opinion on Chemicals and the Water Framework Directive: Technical Guidance for Deriving Environmental Quality Standards, 16 September 2010

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