Scientific Committee on Health, Environmental and Emerging Risks
SCHEER

Scientific Opinion on "Draft Environmental Quality Standards for Priority Substances under the Water Framework Directive"

Diclofenac

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by written procedure on 2 August 2022

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ABSTRACT

For the draft dossier on Environmental Quality Standards on diclofenac, the SCHEER offers the following opinions:

The selected diclofenac MAC QS presented in the dossier does not seem to have been correctly identified from the ecotoxicity dataset and the SCHEER proposes a **MAC $QS_{fw\ eco}$ of 246 µg L^{-1}** (**rounded to 250 µg L^{-1})** and a **MAC $QS_{sw\ eco}$ of 29 µg L^{-1}** as alternatives. Regarding deriving the AA-QS, individually neither the deterministic approach, using the mesocosm study by Joachim et al (2021), nor the probabilistic approach using the SSD could be said to be satisfactory on their own (study reliability and poor fit of curve). But by taking a weight of evidence approach including considering the NOEC of the community response in the mesocosm study and utilising the bulk of chronic data provided, the SCHEER supports the **AA-$QS_{fw\ eco}$ of 0.04 µg L^{-1}** and **AA-$QS_{sw\ eco}$ of 0.004 µg L^{-1}**.

The SCHEER accepts there is no necessity to derive a benthic organism related QS given its high solubility. Given the widespread and serious population effects of diclofenac on Asian vultures (*Gyps bengalensis*), the dossier uses data from these birds to derive **$QS_{biota\ sec\ pois}$ of 1.16 µg kg^{-1}** (rounded to **1.2 µg kg^{-1}**) for mussels and using a BAF of 216 L kg^{-1} this translated to a **$QS_{biota\ sec\ pois}$ of 0.0054 µg L^{-1}**. Given the starting point of an ADI provided by EMA, a QS to protect human health with respect to fish consumption of **$QS_{biota\ hh}$** of **61.35 µg kg^{-1} $_{biota\ ww}$** (rounded **61 µg kg^{-1}**) was calculated. To protect human health from drinking using the same ADI led to a **$QS_{dw\ hh}$ of 3.5 µg L^{-1}** being offered. Both of these human health QS are endorsed by the SCHEER.

The lowest EQS value is the **AA-$QS_{sw\ eco}$ of 4 ng L^{-1}**, however, the **$QS_{biota\ sec\ pois}$ of 5.4 ng L^{-1}** would be more difficult to achieve in fresh water and therefore could be considered the most critical.

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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 (EQS) 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 EQS for those substances were established (Directive 2008/105/EC or EQS Directive, EQSD). WFD Article 16 requires the Commission to periodically review the list. The first review led to a Commission proposal in 2011, resulting in the adoption of a revised list in 2013 containing an additional 12 Priority Substances. Technical work to support a second review has been underway for some time, and several substances have been identified as possible candidate Priority Substances. The Commission will be drafting a legislative proposal, with the aim of presenting it to the Council and the Parliament sometime around mid-2022.

The technical work has been supported by the Working Group (WG) Chemicals under the Common Implementation Strategy for the WFD. The WG is chaired by DG Environment and consists of experts from Member States, EFTA countries, candidate countries and several European umbrella organisations representing a wide range of interests (industry, agriculture, water, environment, etc.).

Experts nominated by WG Members (operating as individual substance Expert Groups and through the Sub-Group on Review of Priority Substances, SG-R) have been deriving EQS for the possible candidate substances and have produced draft EQS for most of them. In some cases, a consensus has been reached, but in others there is disagreement about one or other component of the draft dossier. The EQS for a number of existing priority substances are currently also being revised.

The EQS derivation has been carried out in accordance with the Technical Guidance Document on Deriving EQS (TGD-EQS) reviewed by the SCHEER[1].

2. TERMS OF REFERENCE

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

1. Whether the EQS have been correctly and appropriately derived, in the light of the available information and the TGD-EQS;
2. Whether the most critical EQS (in terms of impact on environment/health) have been correctly identified.

Where there is disagreement between experts of WG Chemicals or there are other unresolved issues, we ask that the SCHEER consider additional points, identified in the cover note(s).

For each substance, a comprehensive EQS dossier is or will be available. DG Environment is providing three EQS dossiers ahead of the 3-4 March SCHEER Plenary and expects to provide most of the remaining dossiers over the next three months. The dossiers contain much more information than simply the draft EQS; the SCHEER is asked to focus on the latter.

[1] https://circabc.europa.eu/ui/group/9ab5926d-bed4-4322-9aa7-9964bbe8312d/library/ba6810cd-e611-4f72-9902-f0d8867a2a6b/details

In some cases, especially where additional points are raised, additional documents may be provided. Some of the studies referred to in the dossiers are not publicly available. If the SCHEER needs to see these studies, it is invited to please contact DG Environment.

In the case of diclofenac the following questions are posed to the SCHEER:

All potential ways determining an EQS independently, the (i) deterministic approach (ii) the use of the mesocosm results and (iii) the secondary poisoning calculations are leading to the same magnitude, which in the view of the majority of the expert group gives an additional trust on the values.

The majority of the expert group decided, after intense discussions, that the EQS setting should be based on a mesocosm experiment conducted at INERIS, France (Joachim et al. 2021, https://doi.org/10.1016/j.ecoenv.2020.111812). A minority voice/ vote against this decision was raised by the stakeholder affiliated to GSK, the main marketing authorisation holder (MAH) of diclofenac. Other stakeholders agreed with the majority views.

For the deterministic approach the majority of experts agreed to include the results from the mesocosm caged mussel study. Due to the specific study design the study can be compared to laboratory derived results. However, the deterministic approach is not relevant for deriving the EQS for diclofenac anyway.

For several taxonomic groups and in one case even for the same species relatively large discrepancies exist between bioconcentration determined under laboratory conditions and bioaccumulation determined in field conditions. For this reason, the BAF values obtained from the field studies were used to determine the bioconcentration and bioaccumulation of Diclofenac.

As mentioned in detail in the dossier, an SSD could not be derived. The distribution of the EC10 and NOEC values is multimodal. These results suggest the SSD approach may not be applicable to the whole dataset. However, no mechanistic explanation for a sensitive subgroup could be identified and the SSD may also not be applicable to the sensitive subgroup as there is no mechanistic explanation why some species are more sensitive than other. In contrast to e.g., substances with an estrogenic mode of action, for Diclofenac there are no clear taxonomic related differences found in the distribution of the SSD.

The topics GSK mentioned in its review submitted directly to the SCHEER Committee, outside normal procedures, are considered in detail in the draft dossier and reflected in these questions above. All of the mentioned aspects by GSK were discussed in various online meetings in lengthy details. The submitted draft dossier reflects the opinion of the majority of the experts, including other stakeholders.

The review submitted from GSK constitutes a 'dissenting view', which is not sufficiently backed up by scientific data, according to the other members of the Working Group. In addition, it should be noted that GSK is the owner of diclofenac and the main marketing authorisation holder for Diclofenac containing products in Europe, and therefore their views could (partly) constitute a conflict of interest.

3. OPINION

It should be noted that in a separate synthesis Opinion to be finalised, the SCHEER provides an analysis of weaknesses and unresolved issues common to all dossiers and discusses the risk assessment method. This Opinion provided by SCHEER will therefore be restricted to issues directly associated with the derivation of the different EQS.

Specific comments on the different sections of the dossier are listed below.

Section 6. Effects and quality standards

Section 6.2. Acute aquatic ecotoxicity

Deterministic approach

The most sensitive values for acute toxicity include 9,500, 9,560, 7,800, 6,300, 6,230, 6,110, 4,200 and 2,919 µg L^{-1} for crustacean, platyhelminth, fish and amphibian, none scoring higher than a reliability score of 2. The dossier identifies the lowest LC50 value in the acute freshwater dataset as 4,200 µg L^{-1} for embryo mortality of *Dugesia japonica.* The lower, more sensitive LC50 value of 2,919 µg L^{-1} is for a saltwater mysidacea. On p 47 the dossier explains that where there is no statistically significant difference between freshwater and marine datasets, all the ecotoxicity data may be pooled. That being the case, the SCHEER does not agree with the selection of 4,200 µg L^{-1} to derive the MAC. In the dossier it is explained that as short-term tests from three trophic levels are available, an Assessment Factor (AF) of 10 could be applied, which leads the dossier to a MAC-$QS_{fw, eco}$ 420 µg L^{-1}. However, if we use the most sensitive organism/effect in the dossier, this should be **MAC-$QS_{fw, eco}$ 246 µg L^{-1}.**

The higher diversity in marine species and the fact that only three marine species are represented in the dataset calls for a higher AF. An additional AF of 10 for marine waters led to a **MAC-$QS_{sw, eco}$ 42 µg L^{-1}** being offered in the dossier, however, using the most sensitive organism/effect in the dossier, which is actually from a saltwater organism, the SCHEER suggests this should be a **MAC-$QS_{sw, eco}$ 29 µg L^{-1}.**

Probabilistic approach

Although diclofenac has a relatively rich dataset, there are insufficient numbers of taxonomic groups so there was no attempt to derive the MAC QS via the SSD approach. The SCHEER agrees with this.

Section 6.3 Chronic aquatic ecotoxicity

Deterministic approach

Compared to many pharmaceuticals, there is a relatively large dataset of NOECs and EC10s available for algae, invertebrates, and fish, which, based on the EU EQS guidance (EC 2018), enables an assessment factor of 10 to be applied. The NOEC/EC10 values for algae and plants range from 2 to 52,000 µg L^{-1}, for crustaceans from 40 to 72,000 µg L^{-1}, and for fish from 3 to 71,000 µg L^{-1}. Most of these have a reliability rating of between 1 and 2 and about half only offer a nominal exposure concentration. The dossier says 'The most sensitive

chronic study assessed were *Dreissena polymorpha*, as part of a 5=month mesocosm conducted by Joachim et al. (2021). *As the mussels were exposed in cages, this study can be used as a single species study and used for the deterministic approach.* In reviewing this part of the Joachim et al. (2021) study, the SCHEER noted diclofenac seemed to have little or no impact on end-points, such as condition, energy reserve, amylase activity or immune function except at the highest concentration. However, a relatively higher mortality was highlighted at the effect concentration of 0.44 µg L^{-1} with 40.6%+/-6.0% mortality compared to 29.7% +/-9.6% for the control. The authors report this as significant at $p<0.05$. On this basis, an EC10 value of 0.25 µg L^{-1} is offered. It was confusing that in Annex I, chapter 9 of the dossier, an EC10 of 0.37 µg L^{-1} rather than 0.25 µg L^{-1} is reported. The SCHEER does not consider that the high loss of mussels (almost 1/3rd) in the control was acceptable and they were sceptical that the difference was statistically significant. Therefore, the SCHEER does not endorse the proposed starting point for a deterministic AA-$QS_{fw,eco}$ nor the AA-$QS_{sw,eco}$ proposed on the same conceptual basis.

Probabilistic approach (SSD method)

The amount of data is sufficient to attempt estimating an SSD in order to determine a robust HC5 value. However, the SCHEER notes that Table 6.2 lists 35 reliable results from 21 taxa. The values used for the SSD shown in Table 6.3 are indeed individual values for the 21 separate taxa. But the criteria for the selection of one study of a particular taxa over another are not transparent, given the same reliability factor. In general, the lower value is used without any justification for the choice, even in cases of extremely high differences for the same endpoint (e.g., two studies on *Lemna minor* on 7-10 days growth with a NOEC/EC10 of 1.7 and 3140 µg L^{-1} respectively; two studies on *Danio rerio* on 28-30 days growth with a NOEC/EC10 of 8.6 and 5000 µg L^{-1} respectively). Looking carefully at the data selected and at Annex 1 of the dossier where the chronic studies are summarised, the SCHEER noted differences in end-points, some of which were of questionable relevance.

The authors of the dossier did not have confidence that a SSD curve capable of predicting the HC5 was possible due to the multimodality of the curve obtained with the selected NOEC/EC10 values. Rather than discard all the evidence, the DG ENV was asked by the SCHEER to report what the HC5 could be from the imperfect SSD curves. The reported range of HC5 lay between 1.78 to 5.6 µg L^{-1}. If a probabilistic approach were selected, however imperfect, this would offer AA-$QS_{fw,eco}$ of 0.076 to 0.23 µg L^{-1}.

Mesocosm approach

According to the Technical Guidance:

"*Mesocosm studies such as experimental pond or stream systems can also provide a useful line of evidence when choosing a suitable AF*."

Moreover:

"*Analysis of mesocosm or field data may suggest the laboratory-based QS is over-protective (the QS based on laboratory data is lower than the field threshold) and, under these circumstances, Annex V of the WFD would encourage the use of a reduced AF.*"

It is the opinion of the SCHEER that the identified mesocosm study of Joachim et al. (2021), is a useful piece of work, describing an experiment conducted over a very long period (more than 5 months). However, the authors themselves report they were unable to control variables like oxygen between the different treatments and there were problems with high mortalities in the controls. It is the opinion of the SCHEER that the NOECs estimated for parameters at individual level cannot be assumed to be fully reliable, while the NOEC at the population and community level proposed in the conclusion of the paper (0.44 µg/L) may be used as a line of evidence for confirming or revising the EQS derived with deterministic or probabilistic procedures. With an AF of 10, this would give an AA-$QS_{fw,eco}$ of 0.04 µg L^{-1}.

Summary of SCHEER position on AA-QS

The TGD advises that the more reliable approach, whether it be probabilistic or deterministic, be used exclusively to derive an EQS (either/or). However, in the case of diclofenac, neither line of evidence on its own was convincing. In such circumstances, the SCHEER recommends a weight of evidence approach be used whereby lines of evidence from all approaches be considered. In the case of diclofenac, we could have a AA-$QS_{fw,eco}$ of 0.04 µg L^{-1} derived from the mesocosm study and AA-$QS_{fw,eco}$ of 0.076 to 0.23 µg L^{-1} derived from the imperfect SSD (probabilistic approach). Given the need for the regulator to provide a QS that is protective but scientifically defensible, the SCHEER observes that the lower AA-$QS_{fw,eco}$ of 0.076 µg L^{-1} from an SSD is not far from the tentative AA-$QS_{fw,eco}$ of 0.04 µg L^{-1} from the mesocosm study and so could be justified. Therefore, an **AA-$QS_{fw,eco}$ of 0.04 µg L^{-1}** and a **AA-$QS_{sw,eco}$ of 0.004 µg L^{-1}** could now be supported by the SCHEER. Although not currently part of the TGD, the SCHEER recommends that a weight of evidence approach be used in future to arrive at a decision when contradictory data gives a poor fit for an SSD and when the credibility of a contentious study offered for a deterministic approach is doubtful.

Section 6.5: Sediment ecotoxicology

Given that diclofenac is an acid which dissociates at neutral pH into an anion (pKa approximately 4), it is reasonable to accept that it would be unlikely to bind to sediment. Table 5.1 shows a Koc of 1-2 L kg^{-1} at neutral pH values, which supports the argument that sediment binding would not be significant. The SCHEER, therefore, agrees that there is no necessity to derive a $QS_{sediment}$.

Section 6.6 Secondary Poisoning

Considering the data on LogKow (higher than 3) and the BAF data (higher than 100), the criteria are met to assess secondary poisoning. The sensitivity of vultures is well known such as *Gyps bengalensis* LD50 0.225 mg kg^{-1}_{bw} $d^{-1,}$ but other birds are more tolerant, the lowest non-vulture value being an LD50 4.1 mg kg^{-1}_{bw} d^{-1}. Using vultures as a standard and given the lack of other bird data, an AF of 100 is recommended (LD10 0.722 ng kJ^{-1} diet). The $QS_{biota\ sec\ pois}$ is calculated for different food items to protect the aquatic ecosystem (fish, bivalves, arthropods, vegetation) with the lowest value (derived for bivalves) being **$QS_{biota\ sec\ pois}$ 1.16 µg kg^{-1}_{diet}** (rounded **1.2 µg kg^{-1}_{diet}**), which are endorsed by the SCHEER.

Bioaccumulation is discussed with respect to the value of field observations over laboratory data. One American and three Chinese field studies are discussed. Due to some issues with the Chinese studies, the dossier uses a BAF of 216 L kg^{-1} for molluscs based on the American study. The $QS_{biota\ sec\ pois}$ 1.16 µg kg^{-1}_{diet} is divided by BAF of 216 L kg^{-1} to generate the equivalent water value of **$QS_{water\ sec\ pois}$ 5.4 ng L^{-1} (0.0054 µg L^{-1}).** The SCHEER endorses these values.

Section 7: Human health

The JRC revised its dossier following information provided by SCHEER on a diclofenac ADI provided by EMA in 2003. This ADI of 0.5 µg $kg_{bw}^{-1}d^{-1}$ was derived from a LOEL of 0.1 mg $kg^{-1}{}_{bw}$ with an AF of 200 applied.

Section 7.1 Human health via consumption of fishery products

Given the starting point of an ADI of 0.5 µg $kg_{bw}^{-1}d^{-1}$ provided by EMA, a QS was made to protect human health with respect to fish consumption. This takes the assumptions outlined in the TGD of a 0.2 fraction of fish in the diet with a 95th percentile consumption of 0.00163 kg_{fish} $kg^{-1}{}_{bw}$ d^{-1} to give a **$QS_{biota\ hh}$ of 61.35 µg kg^{-1} (rounded 61 µg kg^{-1}).** Working back from the BAF of 216 L kg^{-1} (see secondary poisoning above) gives an associated protective level of 0.28 µg L^{-1} in the water, which is endorsed by the SCHEER.

Section 7.2 Human health via consumption of drinking water

To protect human health from drinking water, the ADI of 0.5 µg $kg_{bw}^{-1}d^{-1}$ was once again used taking the assumptions outlined in the TGD of a 0.2 fraction of tap water in the necessary diet of 2 L d^{-1} water intake for a 70 kg body weight. This led to a **$QS_{dw\ hh}$ of 3.5 µg L^{-1}** being offered. This is also endorsed by the SCHEER.

Responses to the specific questions posed in the Terms of Reference

All potential ways determining an EQS independently, the (i) deterministic approach (ii) the use of the mesocosm results and (iii) the secondary poisoning calculations lead to the same magnitude, which, in the view of the majority of the expert group, gives additional credibility to the values.

It is the opinion of the SCHEER that there are problems with the derivation of a QS value using any of the deterministic, probabilistic and mesocosm approaches on their own. This makes the situation difficult since the TGD recommends that the most reliable approach be selected. Nevertheless, if the data is viewed in its entirety, using the principles of weight of evidence, the SCHEER found it could support the AA $QS_{fw\ eco}$ offered in the dossier.

The majority of the expert group decided, after intense discussions, that the EQS setting should be based on a mesocosm experiment conducted at INERIS, France (Joachim et al. 2021, https://doi.org/10.1016/j.ecoenv.2020.111812). A minority voice/ vote against this decision was raised by the stakeholder affiliated to GSK, the main marketing authorisation holder (MAH) of diclofenac. Other stakeholders agreed with the majority view.

It is the opinion of the SCHEER that the mesocosm experiment may be used as one line of evidence.

For the deterministic approach, the majority of experts agreed to include the results from the mesocosm caged mussel study. Due to the specific study design, the study can be compared to laboratory-derived results. However, the deterministic approach is not relevant for deriving the EQS for diclofenac anyway.

It is the opinion of the SCHEER that the mesocosm caged mussel study cannot be used for the deterministic derivation of a QS value, due to the high mortality in the controls and the doubtful statistical evaluation of the data.

For several taxonomic groups and in one case even for the same species, relatively large discrepancies exist between the bioconcentration determined under laboratory conditions and bioaccumulation determined in field conditions. For this reason, the BAF values obtained from the field studies were used to determine the bioconcentration and bioaccumulation of Diclofenac.

The SCHEER agrees with the use of field studies.

As mentioned in detail in the dossier, an SSD could not be derived. The distribution of the EC10 and NOEC values is multimodal. These results suggest the SSD approach may not be applicable to the whole dataset. However, no mechanistic explanation for a sensitive subgroup could be identified and the SSD may also not be applicable to the sensitive subgroup as there is no mechanistic explanation for why some species are more sensitive than others. In contrast to, for example, substances with an estrogenic mode of action, for Diclofenac there are no clear taxonomic-related differences found in the distribution of the SSD.

The SCHEER had concerns over the selection of data for the derivation of the SSD, which should have been better explained in the dossier.

4. CRITICAL EQS

The lowest values are the AA-$QS_{sw\ eco}$ of 4 ng L-1 and the $QS_{biota\ sec\ pois}$ of 5.4 ng L-1. Considering the generally high dilution in the marine environment and taking into account that the $QS_{biota\ sec\ pois}$ has been derived on the basis of data obtained on a particularly vulnerable species, it is the opinion of the SCHEER that this may be considered the critical EQS.

5. LIST OF ABBREVIATIONS

AA-QS	Annual Average Quality Standard
ADI	Acceptable Daily Intake
AF	Application Factor
AMR	Anti-Microbial Resistance
BAF	Bioaccumulation Factor
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
EQS	Environmental Quality Standards
MAC-QS	Maximum Acceptable Concentration Quality Standard
SSD	Species Sensitivity Distribution
TL	Threshold Level

6. REFERENCES

Joachim S., Beaudouin R., Daniele G., Geffard A., Bado-Nilles A., Tebby C., et al. Effects of diclofenac on sentinel species and aquatic communities in semi-natural conditions. Ecotoxicology and Environmental Safety 2021; 211: 15.