Scientific Committee on Health, Environmental and Emerging Risks
SCHEER

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

Erythromycin

The SCHEER adopted this document
via written procedure on 28 February 2022

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ABSTRACT

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

The most sensitive organisms for antibiotics are typically cyanobacteria and here evidence is presented for QS for erythromycin which are in line with expectations so SCHEER can support these. Although a probabilistic approach was possible that would have derived MAC-$QS_{fw,eco}$ of 0.52 µg L^{-1} and a MAC-$QS_{sw,eco}$ of 0.052 µg L^{-1}, the SCHEER supports utilising the alternative result from the deterministic approach which would yield **MAC-$QS_{fw,eco}$ of 1.0 µg L^{-1}** and a **MAC-$QS_{sw,eco}$ of 0.1 µg L^{-1}.**

The deterministic and probabilistic values do not differ largely (less than a factor 2) and the deterministic derived values lie well within the confidence interval of the probabilistic approach. The deterministic derived **AA-$QS_{fw,eco}$ of 0.5 µg L^{-1}** and an **AA-$QS_{sw,eco}$ of 0.05 µg L^{-1}** are endorsed by the SCHEER, but the SCHEER considers an application of the probabilistic approach might still have been possible.

The SCHEER requires the calculations of the sediment EQS, to protect benthic organisms, to be reviewed as they currently do not use the appropriate AA-QS values.

The SCHEER support the **$QS_{Biota,\ sec\ pois,\ fw}$ in fish** of **15 mg kg^{-1}_{ww}** and **4.1 mg kg^{-1}_{ww} for bivalves**, however the decision not to derive such standards for the marine environment needs further justification.

To protect human health, the **$QS_{biota\ hh\ food}$ of 120 mg kg^{-1}** and provisional drinking water **$QS_{dw,\ hh}$** of **7 mg L^{-1}** can be supported by the SCHEER.

TABLE OF CONTENTS

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.

An additional comment regarding erythromycin was:
*There are still some doubts on the **maximum allowable concentration MAC-QS derivation**:*
In the first revision of the draft EQS dossier in 2021, experts of the subgroup on macrolides found that it is not realistic at all that the species sensitivity distribution (SSD) based MAC-QS (0.523) is similar to the deterministic annual average value AA-QS (0.5). Because the MAC-QS represents the acute no effect level, the best option for derivation of the MAC

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

would be to establish an SSD with acute L(E)C_{10} or NOEC values, this would deliver an HC_5 at the acute, no effect level. Comparing the acute HC_5-LC_{10} with the HC_5-LC_{50} gives insight into the assessment factor (AF) to be applied to the latter. However, the JRC pointed out that there was not sufficient data to perform the SSD with acute L(E)C_{10} or NOEC values. Based on the uncertainties in the SSD analysis, the MAC-$QS_{fw,eco}$ of 1 µg/L based on the AF approach is proposed as critical MAC value in the present EQS dossier.

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.

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.

3. OPINION

In a separate synthesis Opinion, the SCHEER provided a general discussion concerning the procedure and derivation of the EQS values and related topics and highlighted unresolved issues and weaknesses that are common to more than one substance and dossier.

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

Section 7. Effects and quality standards

Section 7.1. Acute aquatic ecotoxicity

Deterministic approach

Acute ecotoxicity data are available for three freshwater species, representing the base set (algae, invertebrates and fish). According to the EQS Technical Guidance (EC, 2018), the growth rate endpoint is considered for algal tests to be superior to that of changes in biomass.

For freshwater it was noted that from the acute toxicity dataset, the taxonomic group of algae and cyanobacteria appeared to be much more sensitive to erythromycin compared to the other taxonomic groups. The dossier assumed that freshwater and marine cyanobacteria could be considered to be sufficiently similar so that the ecotoxicity results could be combined. For the freshwater species, the lowest EC50 value was 20 µg L^{-1} whilst for marine species this was 10 µg L^{-1}. If an AF of 10 was applied to the lowest (72-h) EC50 of 10 µg L^{-1} (for the marine algae *Tetraselmis suecica*), this would result in a **MAC-$QS_{fw,eco}$ of 1 µg L^{-1}**.

For marine water, if an AF of 100 was used based on the same data as for freshwater, this would result in a **MAC-$QS_{sw,eco}$ of 0.1 µg L^{-1}.**

Probabilistic approach

The dataset does meet the criteria for construction of a Species Sensitivity Distribution (SSD) as listed in the EQS Technical Guidance (EC, 2018) - the database contains data points of 8 different taxonomic groups and contains more than 15 data points. A HC_5 of 5.2 µg L^{-1} was obtained – based on the entire dataset – when obtaining HC_5 from only the most sensitive species, a value of 2.7 µg L^{-1} was obtained. Finally, the HC_5 value of 5.2 µg

L^{-1} was taken forward in the assessment since the data had a normal distribution.

An AF of 10 for freshwater and an AF of 100 for marine water is used, resulting in MAC-$QS_{fw,eco}$ of 0.52 µg L^{-1} and a MAC-$QS_{sw,eco}$ of 0.052 µg L^{-1}. The SCHEER agrees with this approach and notes that the deterministic and probabilistic approach do not differ largely (less than a factor 2) and the deterministic derived values lies well within the confidence interval of the probabilistic approach (95% CL 0.058– 2.423 µg L^{-1}).

The Commission had a supplementary question for the SCHEER about this issue, regarding the security of a MAC-$QS_{fw,eco}$ of 1 µg L^{-1}. The question or doubt was whether a MAC-value of 0.52 µg L^{-1} (probabilistic approach) would not be too close to the AA-value of 0.5 µg L^{-1} (see section 7.2 below). Therefore, the Commission proposes to ignore the 0.52 µg L^{-1} of the probabilistic approach and accept instead the higher deterministic derived value of 1 µg L^{-1} as the freshwater MAC. The view of the SCHEER was that, whilst there could well be enough data for the probabilistic approach, they note the JRC is of the opinion that there are not enough data. On balance, the SCHEER can agree with the Commission on a preference for the **MAC-$QS_{fw,eco}$ of 1 µg L^{-1}** based on some uncertainties in the probabilistic approach.

Section 7.2. Chronic aquatic ecotoxicity

Deterministic approach

Freshwater: Chronic ecotoxicity data are available for at least three species (normally fish, aquatic invertebrates and algae) representing three trophic levels. Therefore, an AF of 10 could be applied to the lowest EC_{10} (72 h) of 5 µg L^{-1} (Cyanobacteria species *Anabaena sp.* growth) resulting in an **AA-$QS_{fw,eco}$ of 0.5 µg L^{-1}**. This was selected over the probabilistic approach. There was relatively plentiful chronic ecotoxicity data for cyanobacteria (although much came from the less favoured endpoint of biomass) and many of the values were in the 5-10 µg L^{-1} , therefore the SCHEER has sufficient confidence to support this EQS.

Marine water: Results from three freshwater species representing three trophic levels are available in the chronic ecotoxicity dataset, but no ecotoxicity data are available on specific marine species. Therefore, an AF of 100 was chosen, resulting in an **AA-$QS_{sw,eco}$ of 0.05 µg L^{-1}**. The SCHEER is also content with this marine QS.

Probabilistic approach

The dossier argues against using the probabilistic approach because only 7 reliable data points could be plotted, and the guidelines call for 10. But there is an argument that a curve predicted from 7 points could still provide greater confidence then the selection of the single lowest value as advocated in the deterministic approach. It was not clear to the SCHEER whether there were only 7 chronic data points in total or whether these only referred to the three different sensitive species groups. If not, the entire dataset could be used and not only the sensitive species. Some clarification here would be appreciated. The SCHEER views that further consideration should be given to probabilistic calculation here.

Section 7.3. Sediment ecotoxicology

The approach to sediment ecotoxicity is to assume that the effects on free-living organisms in the water column from the chemical will be the same for sediment dwelling organisms. Thus, the approach is to use the relevant water effect concentration and calculate the equivalent level in the sediment. The calculation starts with the AA-$QS_{fw,eco}$ of 0.2 µg L^{-1},which is odd given that the studies reviewed in 7.2. report that this should in fact be 0.5

µg L^{-1}. For the sediment partitioning, this was calculated based on a Koc of 570. It is unclear to the SCHEER if this was the appropriate value given that the dossier cites a value of 1877 L kg^{-1}. This methodology is considered appropriate but the Koc selection and use of a different freshwater ecotoxicity value to the QS requires explanation.

The marine sediment calculation is similar, except that it is based on an AA QS_{sw} of 0.02 µg L^{-1}, which is also odd given the studies reviewed in 7.2. indicate this should in fact be 0.05 µg L^{-1}. The SCHEER would need to receive clarification on why two different values are used. Based on the lack of clarity around the choice of values for AA QS, the SCHEER is reluctant to accept the proposed benthic community sediment level QS of 6.02 and 0.602 µg kg^{-1}.

Section 7.5. Secondary Poisoning

On p 37 (second paragraph) it is stated: "The potential for bioaccumulation of erythromycin is indicated by an experimental value Log K_{ow} of 3.1(US EPA, 2012a), that slightly exceeds the trigger value of 3, and by a field-derived BAF-value for freshwater fish of 4500 L kg^{-1} (Gao et al., 2012) (see table 7.2). Therefore, the criteria triggering an assessment for secondary poisoning are met". The dossier selects a NOAEL value of 200 mg $kg^{-1}{}_{bw}d^{-1}$ subacute study with rabbits as most suitable. The obtained **$QS_{water,biota}$** is calculated using a BAF value of 40 L kg^{-1} from bivalves since the earlier mentioned BAF for fish (4500 L kg^{-1}) is considered not reliable. The application of an AF of 100 to the lowest credible chronic datum resulted in a **$QS_{Biota,\ sec\ pois,\ fw}$ in fish** of **15 mg $kg^{-1}{}_{ww}$** and **4.1 mg $kg^{-1}{}_{ww}$ for bivalves,** which the SCHEER can support.

On p 42 (last paragraph) it is said: "For the marine environment, a separate $QS_{biota,sec}$ for marine water is probably not necessary as erythromycin does likely not biomagnify in small birds or mammals". However, according to the Technical Guidance For Deriving Environmental Quality Standards, for biomagnifying substances, a QS based on a biomagnification factor (BMF) must be derived for protecting top predators that feed on the marine fish-eating predators (like sharks, polar bears or some cetaceans). However, for substances that are not expected to biomagnify within marine food chains, a $QS_{biota,secpois,sw}$ should be derived based on a procedure similar to those used for the $QS_{biota,secpois,fw}$. Therefore, it is the opinion of the SCHEER that the $QS_{biota,secpois}$ for the marine environment should be derived.

Section 7.6. Human health

The dossier states that in the present assessment, only microbiological and pharmacological ADI were available. Therefore, the TL_{hh} was calculated from the $NOAEL_{min}$ (the lowest no observed adverse effect level value from a review of mammalian toxicology data) of 100 mg kg^{-1} bw/day in dogs. The calculations generated a **$QS_{biota\ hh\ food}$ of 120 mg kg^{-1}** which the SCHEER can support. If this is converted to a level that must not be exceeded in the water the fish swim in by using the BAF of 4500 L $kg^{-1}{}_{dw}$, this yields a $QS_{water\ hh\ food}$ of 0.106 mg kg-1. However, section 7.4 of the dossier describes this BAF value as not reliable. The SCHEER therefore cannot support a $QS_{water\ hh\ food}$ of 0.106 mg kg^{-1}.

Where the exposure is through drinking water, the daily uptake of drinking water ($uptake_{dw}$) is assumed to be 2 litres for a 70 kg person (EC, 2018). As for the $QS_{biota,\ hh\ food}$, the TL_{hh} value was derived using the selected NOAEL of 100 mg kg^{-1} bw/day in dogs, and a fraction of 0.2 of the TL_{hh} is allocated to the intake of the substance via drinking water (EC, 2018). This results in a provisional drinking water **$QS_{dw,\ hh}$** of **7 mg L^{-1}** for erythromycin. The SCHEER supports this drinking water standard. Nevertheless, the SCHEER also considers that in order to protect human health, a harmonised approach

based on drinking water limit should be sought for pharmaceuticals, in order to mitigate the risks from chronic exposure to these chemicals.

Section 8. Additional considerations

An important additional consideration with antibiotics, however, is avoiding the promotion of antibiotic resistance. Conceptually this has been viewed as associated with the minimum inhibitory concentration (MIC). Unlike the other antibiotic dossiers, this report does consider the topic for erythromycin. The review by Bengtsson-Palme and Larsson (2016) suggests for erythromycin this should be 1 µg L^{-1} which is supported by Schafhauser et al. (2018), in which case the proposed QS of 0.5 µg L^{-1} should be sufficiently precautionary.

4. LIST OF ABBREVIATIONS

AA-QS	Annual Average Quality Standard
ADI	Acceptable Daily Intake
AF	Application Factor
AMR	Anti-Microbial Resistance
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
BMF	Biomagnification Factor
EC50	Effective Concentration 50%
EQS	Environmental Quality Standards
HC5	Hazardous Concentration 5%
MAC-QS	Maximum Acceptable Concentration Quality Standard
MIC	Minimum Inhibitory Concentration
NOAEL	No Observed Adverse Effect Level
SSD	Species Sensitivity Distribution
TL	Threshold Level

5. REFERENCES

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