Scientific Committee on Health, Environmental and Emerging Risks
SCHEER

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

Clarithromycin

The SCHEER adopted this document
via written procedure on 6 May 2022

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This Opinion has been subject to a commenting period of four weeks after its initial publication (from 7 January 2022 to 7 February 2022). Comments received during this period were considered by the SCHEER. For this Opinion, changes were made in the abstract and in section 6.4 secondary poisoning.

All Declarations of Working Group members are available at the following webpage:
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ABSTRACT

For the draft dossier on Environmental Quality standards on clarithromycin, the SCHEER offers the following opinions:

The **MAC-QS$_{fw}$** of **0.13 µg L^{-1}** and **MAC-QS$_{sw}$** of **0.013 µg L^{-1}** as well as the **AA-QS$_{fw}$** of **0.13 µg L^{-1}** and **AA-QS$_{sw}$** of **0.013 µg L^{-1}** were acceptable to SCHEER because of the relatively strong supporting literature. Unlike the other macrolide antibiotic dossiers, there is no offer of benthic organism quality standards for clarithromycin.

The SCHEER agreed the clarithromycin chemical characteristics should trigger a secondary poisoning standard. On 27th April 2022 the JRC reported to the SCHEER that the QS$_{biota\ ww}$ of 15.7 µg kg^{-1} proposed in the dossier was incorrect. The revised calculations would now lead to **QS$_{Biota,\ sec\ pois,\ fw}$ 4.7 or 1.6 mg kg^{-1} ww** dependent on whether an AF of 10 or 30 is selected. The SCHEER awaits further confirmation of the final decision on AF.

Regarding human health, a **QS$_{biota,\ hh}$** of **172 µg kg^{-1} $_{biota\ ww}$** and an **QS$_{dw,\ hh}$ of 9.8 µg L^{-1}** both derived from an established ADI were endorsed by the SCHEER.

The most critical EQS has been correctly identified as the **AA-QS$_{fw}$** of **0.13 µg L^{-1}**.

The SCHEER is aware that, for many pharmaceuticals, there are limited environmental data on which to base the derivation of EQS. The key reference used for the deterministic method would have benefitted from more information to allow the reliability of the effect value to be better judged.

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.
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.

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.

It is not yet possible for the SCHEER to finalise comments on certain parts of this dossier (secondary poisoning, sediment and some parts on human health) because they are still under consideration, taking into account additional data which has been provided. The dossier authors will re-evaluate these sections and amend the draft opinion as appropriate.

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

Section 6. Effects and quality standards

Section 6.1. Acute aquatic ecotoxicity

Deterministic approach

A relatively large number of studies are available for three different algal species with EC50 values of 2, 6, 7, 11, 12, 12, 20, 37, and 230 µg L^{-1}. However, many of them are judged as not reliable. The one study considered reliable with *Anabaena flos-aquae* had an EC50 growth rate value of 12 µg L^{-1}. The dossier does not discuss the general agreement and similarity of much of the data, which in the opinion of the SCHEER actually lend support and instils some confidence. Instead, the dossier utilises an AF of 100, reflecting its lack of confidence in the data, plus an additional AF due to the likely co-presence of the metabolite 14-hydroxy-clarithromycin. It would be expected that adding an AF of 200 to 12 µg L^{-1} would have given an MAC-QS_{fw} of 0.06 µg L^{-1}. However, the dossier explains it would be illogical to have a MAC-QS_{fw} value lower than the AA-QS_{fw} derived from the chronic data (discussed below) and so it offers instead what it calls a tentative **MAC-QS_{fw} of 0.13 µg L^{-1}**. The SCHEER did not find the discussion of this section fully satisfactory. The SCHEER therefore requests that a fuller discussion of the number of data points, including trophic levels (as described in the guidelines table 3 p 42), be presented so that the context around the decision could be better understood.

Regarding the additional factor of 2 proposed to account for the combined effects of the parent substance and its metabolite 14-hydroxy-clarithromycin, the SCHEER would also like to receive more detailed motivation /justification in the text on this issue.

Section 6.2. Chronic aquatic ecotoxicity

Deterministic approach

The chronic ecotox deterministic approach relies on Baumann et al. (2015) reporting an EC10 growth of 2.6 µg L^{-1} for *Anabaena*. Unfortunately, on reading this paper, only minimal experimental data is given, and no graph is provided, so the SCHEER cannot judge the underlying data behind this EC10. Nevertheless, there is some confidence in that several studies have reported effects down to this concentration, (2.5, 2.6, 3.1, 5, 5.2, 25, 28, 40 µg L^{-1}). Applying an AF of 2 x 10 gave an **AA-$QS_{fw,eco}$** of **0.13 µg L^{-1}**. To protect marine organisms, the same freshwater ecotoxicity value was used with an additional AF of 10 added to give an **AA-$QS_{sw,eco}$ of 0.013 µg L^{-1}**. The SCHEER supports these QS.

Probabilistic approach
Only the deterministic approach was offered and not the probabilistic approach. Given the relatively consistent look of the data shown in the tables, it might have been worth exploring further an SSD, including using the less reliable data to see how it would have compared to the deterministic result. However, the SCHEER agrees that insufficient data are available for a probabilistic approach.

In contrast to azithromycin and erythromycin, where they are provided, the dossier should explain why no QS are offered to protect benthic organisms.

Section 6.4. Secondary poisoning

In table 5.1 log K_{ow} of 0.7-1.8 are reported, which are lower than the log K_{ow} threshold of 3.0. But alternative thresholds to trigger secondary poisoning quality standards are a measured BMF>1 or BCF (BAF) ≥100. The dossier reports that in laboratory studies with sea cucumber and clarithromycin, some organs concentrated with a BCF> 100 (Zhu et al., 2020). This is sufficient to require the development of a secondary poisoning QS. Wildlife oral toxicity data was not available. Data is available for rats and dogs (no apical effects reported nor teratogenicity), giving a NOEL of 4 mg kg^{-1} d^{-1} (in the original dossier this was incorrectly reported and calculated on the basis of this being a NOEC). From this data a protective concentration would be, as of 27th April 2022 the JRC correction given to SCHEER indicates this now should be 47 mg kg^{-1} fish. The JRC now believe an AF of 10 or 30 should be applied to give a **$QS_{Biota,\ sec\ pois,\ fw}$ 4.7 or 1.6 mg kg^{-1} ww** with an equivalent water value of **48.4 or 16.1 µg L^{-1}**, which the SCHEER would endorse when an AF is agreed. The SCHEER had earlier noted that the summary table 3.2 gives the standards as $QS_{Biota,\ sec\ pois,\ fw}$ = 157 µg kg^{-1}) and an equivalent water value of 5.82 µg L^{-1} was different from that in the dossier section 6.4. The JRC has now confirmed to the SCHEER that the values in Table 3.2 were indeed an error and can be disregarded as now are the calculations in 6.4. The new calculations offered by the JRC means this section still needs to be confirmed from the point of view of the AF.

The SCHEER notes that there are significant differences of approach apparent in dossiers (such as the selection of BAF values) dealing with very similar molecules such as the macrolide antibiotics. The SCHEER recommends that WGs commissioned to deal with such similar molecules should harmonise their approaches, where appropriate.

Section 7. Human Health

To protect human health via food consumption, the EU TGD assumes a human consumption of 1.6 g fish kg^{-1} of body weight and, in this case, the published ADI (including safety factors) of 1.4 µg kg^{-1}bw d^{-1} (Khan & Nicell 2015). This was derived based on the occupational exposure limit (OEL) of 1 mg/m^3 (according to the MSDS published by Abbott) with a default safety factor of 100. The resulting **$QS_{biota,\ hh}$** of **171.8 µg kg^{-1} biota ww** (rounded to **172 µg kg^{-1} biota ww)** is endorsed by the SCHEER.

The provisional **$QS_{dw,\ hh}$ of 9.8 µg L^{-1}** was also derived from the ADI value (TLhh) and is also supported by the SCHEER.

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). A review by (Bengtsson-Palme and Larsson, 2016) suggests for clarithromycin a PNEC-MIC of 0.25 µg L^{-1} and a PNEC of of 0.13 µg L^{-1}. So, the EQS would appear to remain protective.

4. CRITICAL EQS

The dossier identifies AA-$QS_{fw\ eco}$ of 0.13 µg L^{-1} as the critical QS. The SCHEER notes that its partner AA-$QS_{sw\ eco}$ of 0.013 µg L^{-1} is lower, so more sensitive. However, the AA-$QS_{sw\ eco}$ is actually derived from the AA-$QS_{fw\ eco}$ with an AF of 10. Given the generally abundant dilution of the marine environment, it is likely that the AA-$QS_{fw\ eco}$ will be the more likely to be exceeded and so could be considered the most critical. In summary, the SCHEER accepts that the AA-$QS_{fw\ eco}$ of 0.13 µg L^{-1} can be considered the critical QS and within the limits of the data available to DG-SANTE, and that this was correctly derived.

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
BMF	Biomagnification Factor
EC10	Effective Concentration 10%
EC50	Effective Concentration 50%
EQS	Environmental Quality Standards
MAC-QS	Maximum Acceptable Concentration Quality Standard
MIC	Minimum Inhibitory Concentration
NOEC	No Observed Effect Concentration
OEL	Occupational Exposure Limit
PNEC	Predicted No Effect Concentration
SSD	Species Sensitivity Distribution
TL	Threshold Level

6. REFERENCES

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