Scientific Committee on Health, Environmental and Emerging Risks
SCHEER

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

Azithromycin

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

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Members of the Working Group are acknowledged for their valuable contribution to this opinion. The members of the Working Group are:

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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 (QS) for "Azithromycin" the SCHEER offers the following opinion:

The most sensitive organisms for antibiotics are typically cyanobacteria and here evidence is presented to generate QS for azithromycin based on these organisms. The SCHEER agrees that there was not enough data to apply a probabilistic approach to derive acute and chronic toxicity related QS. The SCHEER can support the **MAC-EQS$_{fw,eco}$ 0.18, MAC-EQS$_{sw,eco}$ 0.018, AA-EQS$_{fw,eco}$ 0.019 and AA-EQS$_{sw,eco}$ 0.0019 µg L^{-1}** and **benthic community QS of 17 and 1.7 µg kg^{-1}** but with reservations. The SCHEER asks that the report that underpins the deterministic approach is made available to the SC and recommends that data emanating from personal communications are not relied upon in future.

The SCHEER requests that an attempt to provide QS to protect marine organisms from secondary poisoning be offered. The SCHEER requests further information be provided to support the proposal of not providing human health safety consumption limits.

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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.

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). This antibiotic has very little toxicity for invertebrates. However, cyanobacteria are sensitive and toxicity values range from 0.94, 1.8, 3.7, 8.4, 19, 26 to 500 µg L^{-1}. Rather than use the lower 0.94 µg L^{-1} value, the dossier identified the 1.8 µg L^{-1} as more relevant as this value is related to growth rate. According to the EQS Technical Guidance (EC, 2018), the growth rate endpoint is preferred for algal tests over changes in biomass.

For freshwater, an AF of 10 was applied, and for marine water an AF of 100 was used because no data specific to marine species was identified. A **MAC-$QS_{fw,eco}$** of **0.18 µg L^{-1}** for freshwater and a **MAC-$QS_{sw,eco}$** of **0.018 µg L^{-1}** was derived. The SCHEER agrees that these QS are appropriate.

The Mattson (2016) reference provides the key data for the deterministic approach and is described in the reference list as:

Mattson B. (2016): Personal communication with Bengt Mattson (Pfizer AB, Sollentuna, Sweden) concerning ecotoxicological values for Azithromycin. All studies are either OECD or EPA guideline studies and were developed as per GLP. Mail from 20.01.2016 to Muris Korkaric.

This is not a peer-reviewed paper available for the SCHEER. The SCHEER does not accept that personal communications are suitable for the derivation of EQS. The SCHEER request that when such a reference is central to the derivation of an EQS, such as in the deterministic approach, the report is provided to the SCHEER. Nevertheless, the result lies within the range of other authors, so this reduces the concern of the SCHEER in this particular instance.

Probabilistic approach

The dataset does not meet the criteria for construction of a Species Sensitivity Distribution (SSD) as listed in the EQS Technical Guidance (EC, 2018) - the database should contain preferably more than 15 data points, and at least 10 data points, from different species covering at least eight taxonomic groups – which was not the case.

Section 7.2. Chronic aquatic ecotoxicity

Deterministic approach

Chronic ecotoxicity data are available for four species, representing three trophic levels, and includes species from the most sensitive taxonomic group. For algae, the data reports are 0.19, 0.33, 1.8 and 5.2 µg L^{-1} EC10 or NOEC for growth rate and 4.4 µg L^{-1} for Daphnia reproduction. With an AF of 10 added to the lowest NOEC of 0.19 µg L^{-1} of growth rate for the cyanobacteria species *Microcystis aeruginosa,* this resulted in an **AA-$QS_{fw,eco}$ of 0.019 µg L^{-1}** and with an additional AF of 10 for marine organisms giving an **AA-$QS_{sw,eco}$** of **0.0019 µg L^{-1}** (no ecotoxicity data for marine organisms are apparently available).

Once again, the chronic ecotox deterministic approach relies on Mattson B. (2016), presumably from the same experiment as used for the acute toxicity EC50 but in this case using the NOEC, see the comments above in section 7.1. Most of the chronic ecotoxicity data reported in the dossier do not come from the peer-reviewed literature. The SCHEER cannot evaluate the reliability of these studies. Nevertheless, the SCHEER can accept these EQS as reasonable given the limited data available.

Probabilistic approach

Insufficient data were available to draw an SSD, so this approach could not be used.

Section 7.3. Sediment ecotoxicity

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 to calculate the equivalent level in the sediment. The calculation starts with the AA-$QS_{fw,eco}$ of 0.019 µg L^{-1} which is appropriate from the studies reviewed in 7.2. For the sediment partitioning, this must be calculated based on the $logK_{oc}$ of the compound, which in this case was taken as 4.25 which reflects the soil literature, and assuming a standard sediment organic content of 0.05 kg kg^{-1}. This methodology is considered appropriate and the **Benthic community freshwater QS of 17 µg kg^{-1}** is accepted by the SCHEER.

The marine sediment calculation is similar, only based on an AA-$QS_{sw,eco}$ of 0.0019 µg L^{-1} which is also appropriate. The SCHEER is satisfied with the proposed **benthic community QS for marine environments of 1.7 µg kg^{-1}**. It should be noted that there remain some caveats regarding the key aquatic ecotoxicity data reference of Mattson (2016).

Section 7.5. Secondary Poisoning

If the log K_{ow} threshold of 3.0 is met or the alternative thresholds of a measured BMF>1 or BCF (BAF) ≥100 are reported, then this will trigger establishing secondary poisoning quality standards. Considering the data on Log K_{ow} (higher than 3) and the BCF and BAF data (higher than 100), the criteria are met to assess secondary poisoning.

The QS_{biota} was calculated from an oral mouse LD_{50} of 3000 mg kg^{-1} (which was not considered ideal, and, furthermore, no valid NOAEL was identified). Subsequently, secondary poisoning was calculated for both, bivalves and fish resulting in a $QS_{Biota,secpois,fw}$ 1.8 mg kg^{-1} for bivalves and 6.6 mg kg^{-1} for fish (the higher value for fish is to be expected based on their lower moisture content and higher energy content).

No QS are offered to protect secondary poisoning in marine organisms. 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

It is reported that no TL_{hh} or reliable NOAEL could be identified, therefore no $QS_{biota,hh}$ was derived.

The SCHEER questions whether no NO(A)EL or LOAEL could be extracted from the identified studies to be used as a point of departure.

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 azithromycin this would be 16 µg L^{-1} and they offer a PNEC of 0.25 µg L^{-1}, in which case the proposed an **AA-$QS_{fw,eco}$ of 0.019 µg L^{-1}** would be protective.

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
EC10	Effective Concentration 10%
EQS	Environmental Quality Standards
LD50	Lethal Dose 50%
LOAEL	Lowest Observed Adverse Effect Level
MAC-QS	Maximum Acceptable Concentration Quality Standard
MIC	Minimum Inhibitory Concentration
NOAEL	No Observed Adverse Effect Level
PNEC	Predicted No Effect Concentration
SSD	Species Sensitivity Distribution
TL	Threshold Level

5. REFERENCES

Bengtsson-Palme J, Larsson D G J (2016). Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. Environment International, 86: 140-149.

EC (European Commission) (2018). Technical Guidance for Deriving Environmental Quality Standards (TGD-EQS). Common Implementation Strategy for the Water Framework Directive. Guidance Document No. 27 Updated version 2018.

Mattson B. (2016). Personal communication with Bengt Mattson (Pfizer AB, Sollentuna, Sweden) concerning ecotoxicological values for Azithromycin. All studies are either OECD or EPA guideline studies and were developed as per GLP. Mail from 20.01.2016 to Muris Korkaric.