



**Scientific Committee on Health, Environmental and Emerging Risks
SCHEER**

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

Carbamazepine



The SCHEER adopted this document
by written procedure on 20 May 2022

ACKNOWLEDGMENTS

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This Opinion has been subject to a commenting period of four weeks after its initial publication (from 21 February to 22 March 2022). Comments received during this period were considered by the SCHEER. For this Opinion, no change was made in the text.

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

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Keywords: carbamazepine, Water Framework Directive, environmental quality standards

Opinion to be cited as:

SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Final Opinion on Draft Environmental Quality Standards for Priority Substances under the Water Framework Directive - carbamazepine, 20 May 2022

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PDF ISSN 2467-4559 ISBN 978-92-68-06297-5 doi:10.2875/86251 EW-CA-23-019-EN-N

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ABSTRACT

Given the necessity to use a deterministic approach to derive the water, marine and sediment EQS, the SCHEER does not accept that the Chen et al (2019) reference is sufficiently reliable to support these quality standards. Using the information in the dossier, the SCHEER would propose alternative **MAC-QS_{fw} of 1.6 mg L⁻¹** and an **MAC-QS_{sw} of 0.16 mg L⁻¹**. Similarly, data from the same Chen et al (2019) study was used to underpin the AA-QS which SCHEER also found unsatisfactory. Using the information in the dossier, the SCHEER would propose instead the alternative AA-QS_{fw} of **0.0025 mg L⁻¹** (or **2.5 µg L⁻¹**) and **AA-QS_{sw} of 0.00025 mg L⁻¹** (or **0.25 µg L⁻¹**). Given these new proposed EQS we request that new benthic organism (sediment) QS be calculated by the Commission.

The calculated **QS_{biota,hh,food} is 19.6 µg kg⁻¹**. It is the opinion of the SCHEER that the latter is most suitable for determining the QS for human health. Therefore, the SCHEER suggests a **QS_{water,hh, food} of 7.0 µg L⁻¹**. The SCHEER proposes a **QS_{dw, hh}=0.54 µg L⁻¹**. This value is below the **AA-QS_{fw} of 2.5 µg L⁻¹**, and so this would necessarily become the most sensitive/appropriate QS for freshwater.

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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 SCHEER¹.

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

The opinion provided by SCHEER will be restricted to issues directly associated with the derivation of the different EQS. The SCHEER will provide a commentary on other aspects of the dossiers, such as on monitored concentrations and risk assessments in a separate synthesis document.

Section 7. Toxicity and setting quality standards

Section 7.1 Acute aquatic ecotoxicity

Deterministic approach

The values shown in Section 7.1 for acute toxicity are in the order of tens of mg L⁻¹, so it is not very acutely toxic. It is reassuring that the acute toxicity values are 10-fold or more above what one might expect in wastewater effluent. Given the relative paucity of ecotoxicity data, the dossier uses the deterministic method to derive an EQS. The key text for the proposed MAC-QS_{fw} appears based on one paper on *Daphnia* (Chen et al., 2019). An assessment factor (AF) of 100 was applied to the lowest (96 h) EC₅₀ of 0.86 mg L⁻¹ for the endpoint of molting, measured for the freshwater crustacean species *Daphnia similis* (Chen et al., 2019), resulting in a **MAC-QS_{fw} of 0.0086 mg L⁻¹ or 8.6 µg L⁻¹**. It was decided to apply an AF of 100 because no studies on acute toxicity of carbamazepine on insects were reported. It is presumed that the reference to insects is to insects that go through a freshwater larval stage, such as ephemoptera, plecoptera and tricoptera. The toxicity database is dominated by plants, algae, crustacea and fish.

The procedure followed by the dossier was based on the paper of Chen et al. (2019) and focused on the molting end-point. This endpoint was considered relevant according to two assumptions:

- Molting is a sub-lethal endpoint and there was no increased mortality during the timespan of the study. However, the endpoint is relevant for derivation of the MAC-QS_{fw} because it is related to growth and reproduction and the purpose of the MAC is to protect the aquatic ecosystem from any effects, including delayed effects, due to short-term concentration peaks.
- The effect on molting on *D. similis* may be indicative of an increased sensitivity in insects. The SCHEER believes this suggestion requires greater justification.

The SCHEER made a careful review of the Chen et al. (2019) study, which is so important to the proposed quality standards. This work studied the effect of carbamazepine on molting, growth and reproduction on *D. similis*, as one of the main crustacean species in Lake Taihu in China. The acute toxicity test (96h) was performed following the OECD test guideline 202, looking at survival and molting. Animals were exposed to six nominal concentrations of carbamazepine (6.25, 12.5, 25, 50, 100, and 200 µg L⁻¹). Molting was examined by counting the shed carapaces. No lethality was observed, while less than 3% mortality was reported at all tested carbamazepine concentrations. Molting frequency was not clearly reduced until 96 h but had not occurred after either 48, and 72 h at 200 µg L⁻¹, which was the highest concentration.

The EC₅₀ 96 h, (864.38 µg L⁻¹) was calculated with SPSS software using the probit method, based upon the concentration-response curve. However, the calculated EC₅₀ is much higher than the highest concentration tested and the obtained value is the result of an extrapolation.

In the Chen et al (2019) study, no effects were seen apart from at the highest treatment at 200 µg L⁻¹ (30% reduction after 96 h looking at 30 individuals) and the concentration was not measured apart from at t=0. Therefore, the paper does not have a dose response curve to follow (since only the highest value was effective). The authors instead used a model to predict the EC₅₀ as likely to be 864 µg L⁻¹ for this end-point, for which an AF of 100 was applied to give an MAC-QS of 8.6 µg L⁻¹ as proposed in the dossier. It was noteworthy that the effects observed by Chen et al (2019) were two orders of magnitude below those found for other freshwater crustacea, including other cladoceran species. Comparable differences (two to three orders of magnitude) are also evident between the 21-day NOEC on reproduction reported by the Chen et al study and the NOEC on cladoceran reproduction reported in other three studies. The results of the Chen et al (2019) study seems to be an outlier. Moreover, the two basic assumptions for the procedure of the dossier are not sufficiently supported.

In summary, the SCHEER does not accept that the Chen et al (2019) reference is suitable for the derivation of the MAC-QS_{fw}.

As an alternative, the SCHEER would propose the EC₅₀ of 15.52 mg L⁻¹ reported for *Hydra attenuata* by Quin et al (2008) be used as the basis for this EQS. Whilst it was given a 2nd class reliability score in the dossier, it is close to the 20 mg L⁻¹ LC₅₀ reported for *Oncorhynchus mykiss* (Li et al., 2011). Therefore, applying an AF of 100, as in the dossier, would give a MAC-QS_{fw} of 0.155 mg L⁻¹. However, there is an argument that since the ecotoxicity database contains information on algae, invertebrates and fish, an AF of 10 could be considered sufficient rather than an AF of 100. The SCHEER is doubtful that there is an exceptional case for carbamazepine requiring an AF of 100 because of the single questionable study looking at molting in a crustacean. If an AF of 10 is used instead, this would lead to a **MAC-QS_{fw} of 1.55 mg L⁻¹**. The SCHEER, therefore, offers **MAC-QS_{fw} of 1.55 mg L⁻¹** (rounded at **1.6 mg L⁻¹**) as the most appropriate, given that data is available for freshwater algae, plants, crustacea and fish, meaning a lower AF of 10 can be accepted.

The dossier also proposes relying on the same Daphnia freshwater study (Chen et al., 2019) for the marine environment only increasing the AF from 100 to 500, so giving a marine MAC-QS of 1.7 µg L⁻¹. However, the SCHEER does not accept that the Chen et al (2019) reference is suitable for deriving either the MAC-QS_{fw} or MAC-QS_{sw}. Reviewing the information provided in the dossier for the marine environment, information is provided on a bacteria, an alga, a rotifer and a crustacean with EC₅₀ of 65, 295, 139 and 59 mg L⁻¹ (but no fish). The lowest reported effect was the LC₅₀ of 59 mg L⁻¹ for *Tisbe battagliai* by Trombini et al (2016). The SCHEER agrees with the dossier that given the modest amount of marine ecotoxicity available, the lowest freshwater effect level could be used, which in this case is the EC₅₀ of 15.52 mg L⁻¹ reported for *Hydra attenuata* by Quinn et al (2008) for this Marine EQS. Therefore, the SCHEER recommends adding the additional marine AF of 10 to the **MAC-QS_{fw} of 1.6 mg L⁻¹** to give a **MAC-QS_{sw} of 0.16 mg L⁻¹**.

Probabilistic approach

The dossier admits that insufficient data exists to use the ideal probabilistic approach for either acute or chronic toxicity using an SSD to select a quality standard.

Section 7.2. Chronic aquatic ecotoxicity

There are several papers available on *Daphnia* reproduction with the key text being

'An AF of 10 is only sufficient when the species showing the lowest long-term toxicity result can be considered to represent one of the more sensitive groups (EC, 2018). As indicated above, insects are not represented in the dataset, whereas they may be sensitive to carbamazepine. In this case, the TGD (EC, 2018) states that an assessment factor of 50 should be applied to take into account any interspecies variation in sensitivity. Therefore, an AF of 50 was applied to the lowest NOEC (21 days) of 0.0003 mg/L (0.3 µg/L) for *D. similis* for the endpoint of fecundity corresponding to the mean number of broods per female for the freshwater crustacean *Daphnia similis* (Chen et al., 2019)'.

The argument proposed in the dossier, therefore, is that as insect (larva) could be the most sensitive freshwater group (based on the Chen et al, 2019 acute experiment that found an apparent effect on molting), they should increase the AF from 10 to 50. This resulted in an AA-QS_{fw,eco} of 0.000006 mg L⁻¹ (6 ng L⁻¹). This proposal in the dossier, of moving the AF from 10 to 50, is very dependent on the credibility of the Chen et al (2019) study. It should be noted that, as mentioned above, the author Chen et al (2019), is reporting effects two orders of magnitude below any of the other crustacean observations in the literature. The dossier assumes this is reliable and that *Daphnia similis* must be 100-fold more sensitive than other *Daphnia* species. Whilst this is not impossible, the SCHEER would expect the study to provide extremely convincing evidence. When this paper is read, it reveals that in the experiment, there were only 6 females in each treatment and at 3 µg L⁻¹, the lowest effect concentration, the mean number of broods per female dropped from 9 to 8 which was seen as significant at p<0.05. Having only 6 females in a treatment, we are in effect comparing a likely total of 48 hatchlings compared to 54. This single experiment shows an extremely modest effect, with mean difference of only 48 to 54 (6) hatchlings, so it does not seem convincing to present it as being significant.. It would be expected that detecting such a small effect would require much higher numbers of individuals or multiple repeated similar tests.

In summary, the SCHEER does not accept that the Chen et al. (2019) reference is suitable to derive the AA-QS_{fw}.

As an alternative, the SCHEER would propose that the NOEC of 0.025 mg L⁻¹ reported for *Ceriodaphnia dubia* by Ferrari et al (2004) could be used as the basis for this EQS. Whilst it was given a 2nd class reliability score in the dossier, it is close to the 0.1 mg L⁻¹ NOEC reported for *Daphnia pulex* (Lürling et al., 2006) and also to values for several algae. Therefore, applying an AF of 50, as in the dossier, would give an **AA-QS_{fw} of 0.0005 mg L⁻¹ (or 0.5 µg L⁻¹)**. However, if the argument for an AF of 50 is disregarded, due to the doubts over the Chen et al (2019) study, then an AF of 10 would be more consistent, in which case an **AA-QS_{fw} of 0.0025 mg L⁻¹ (or 2.5 µg L⁻¹)** would be recommended by the SCHEER.

For the marine environment, the lowest reported effect was an EC10 of 5.27 mg L⁻¹ for *Crassostrea gigas* by Di Poi et al (2019). Given the lack of chronic marine ecotoxicity data, it would be reasonable to follow the logic of the dossier and use the lowest freshwater effect at 0.025 mg L⁻¹, which, with an additional AF of 10, gives an **AA-QS_{sw} of 0.00025 mg L⁻¹ (or 0.25 µg L⁻¹)**. A recent review of the sensitivity of marine bivalves (Almeida et al., 2021) has indicated that a few reports show some oxidative stress effects down to 0.1 µg L, suggesting this topic requires further review and perhaps a lower QS is required.

Section 7.3 Sediment ecotoxicity

The approach to sediment ecotoxicity is to assume that the effects of the chemical on free-living organisms in the water column 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. It might be expected this would start with the **AA-QS_{fw,eco} of 0.000006 mg L⁻¹ (6 ng L⁻¹)**, but instead the value 0.0005 mg L⁻¹ was used and the reason for doing so was not made clear.

For the sediment partitioning, this must be calculated based on the Koc of the compound and assuming a standard sediment organic content. This methodology appears appropriate, but the freshwater ecotoxicity value chosen appears odd. It is presumed the value was based on the Chen et al. (2019) study, which the SCHEER rejects, and so this benthic community QS of 9.8 µg kg⁻¹ must also be questioned.

The marine sediment calculation is similar, only it is based on an AA EQS_{sw} of 0.00002 mg L⁻¹ rather than the AA EQS_{sw} of 0.000006 mg L⁻¹, which is hard to follow. Given the doubts over the Chen et al (2019) study, the SCHEER would also be unwilling to approve this value. The SCHEER would recommend a re-calculation based on the alternative AA EQS recommended above.

Section 7.5 Secondary poisoning

Considering the physical-chemical properties of the substance and, in particular, that the logKow is below the trigger value of 3, no secondary poisoning assessment was undertaken in the dossier. The SCHEER agrees with this approach.

Section 7.6 Human health

For the human health risk *via* consumption of fishery products, the dossier uses as TL_{hh} the NOAEL of 0.016 mg.kg⁻¹_{bw}.d⁻¹. It is the opinion of the SCHEER that this is not correct and, according to the EQS Technical Guidance (EC, 2018), it should be reduced by an AF of 100. So, the TL_{hh} should be 0.16 µg kg⁻¹_{bw} d⁻¹.

According to the EQS Technical Guidance:

$$QS_{\text{biota, hh, food}} (\mu\text{g kg}^{-1} \text{ biota}) = 0.2 \cdot TL_{\text{hh}} (\mu\text{g kg}^{-1} \text{ bw d}^{-1}) / 0.00163$$

Therefore, the calculated **QS_{biota, hh, food} is 19.6 µg kg⁻¹**.

Then, to convert into a water column concentration standard, the QS_{biota, hh, food} has to be divided by the BAF. The dossier suggests using the BAF for liver in fish reported in Garcia et al. (2012), equivalent to 3.8. The same study reports a BAF for muscle of 2.8. It is the opinion of the SCHEER that the latter is most suitable for determining the QS for human health. Therefore, the SCHEER suggests a **QS_{water, hh, food} of 7.0 µg L⁻¹**.

Regarding exposure *via* drinking water, the dossier refers to the value proposed by Moermond (2014) of a **QS_{dw, hh}=54 µg L⁻¹**. This value was obtained using an ADI of 15.5 µg kg⁻¹_{bw} d⁻¹. This value of ADI is 100 times higher than the TL used for the QS_{biota, hh, food}. Probably it is the same NOAEL reported above and should be reduced by an AF of 100. Accepting the same TL_{hh} used for the QS_{biota, hh, food}, the SCHEER proposes a **QS_{dw, hh}=0.54 µg L⁻¹**. This value is below the **AA-QS_{fw} of 2.5 µg L⁻¹**, and so it may be considered the most sensitive/protective QS for freshwater.

In addition to the disagreements already mentioned for the derivation of the QSs, the SCHEER would like to highlight that in the human health section of the dossier, there are

calculation errors and inconsistencies in the calculation of the $QS_{\text{biota, hh, food}}$ and of the $QS_{\text{water, hh, food}}$.

4. 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 Limit

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