Scientific Committee on Health, Environmental and Emerging Risks
SCHEER

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

Ibuprofen

The SCHEER adopted this document
via written procedure on 5 December 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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This Opinion has been subject to a commenting period of four weeks after its initial publication (from 21 September to 20 October 2022). Comments received during this period were considered by the SCHEER. For this Opinion, main changes were made in sections 7.5.2, 7.7 and 9, in point 4 as well as in the abstract.

The SCHEER provided corrections for **AA-QS$_{sw, eco}$ = 0.014 µg L^{-1}** (based on the NOEC for *D. rerio* of 6.88 µg L^{-1}) in section 7.5.5 and in the abstract, after publication of the text. This **CORRIGENDUM** was adopted by the SCHEER on 26 January 2023

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ABSTRACT

The dossier on Environmental Quality Standards for "Ibuprofen" is reviewed by the SCHEER according to the general mandate on EQS dossiers.

The proportion of the ibuprofen molecule that becomes neutral (hydrophobic), associated with higher uptake into cells, increases as the pH decreases. Whilst it is considered that 93% of European waterbodies are >pH 7, it is necessary that the Commission develops standards that are protective of all European waterbodies. The SCHEER, therefore, considers it appropriate that some way of extrapolating test data to a waterbody of a lower pH, i.e. of higher risk is made.

The SCHEER is in agreement with the comments in the dossier that no reliable acute study can be identified which may be used to derive an EQS. Therefore, also the derivation of an $MAC_{fw,eco}$ is not possible.

A NOEC of 55 µg L^{-1} was identified for *Danio rerio*, normalised to a NOEC for pH 6.5 as 6.88µg L^{-1}. The SCHEER accepts an AF of 10 could be used as a starting point – since also values for algae and crustacea were identified – and increased with an additional AF of 5 since relevant end-points like gonadal development were not included (giving a total AF of 50). Therefore, starting from the NOEC for *Danio rerio* of 6.88 µg L^{-1} (pH corrected) a **$AA\text{-}QS_{fw,eco}$ of 6.88/50 = 0.138 µg L^{-1}** (rounded to **0.14 µg L^{-1}**) is derived. With an additional AF of 10, a **$AA\text{-}QS_{sw,eco}$ = 0.014 µg L^{-1}** is derived.

The SCHEER questions the derived $QS_{water,secpois}$. The original correction factor (CF) was calculated as Ratio logD1/logD2 = 3.68 which was contradicted in section 3.4, where to calculate the CF = $10^{\Delta \log D}$ with Δ log D = log D1 - log D2, led to a CF of 21.88, leading to a $QS_{water,secpois}$ = 0.064 µg L^{-1}.

~~B~~based on an identified ADI of 110 µg kg_{bw}^{-1} d^{-1}, a $QS_{biota\ hh}$ of 13.5 mg kg_{biota}^{-1} could be calculated for fish consumption. The SCHEER endorses this value.

The SCHEER agrees that a general conclusion on the toxicity of transformation products is not possible at the present state due to missing information on the complex degradation pathways.

Although a TL_{hh} is available, as there is no proposed value in the bioaccumulation section, the SCHEER agrees that no $QS_{hh,biota}$ can be determined.

The critical EQSs are the **$QS_{water,secpois}$ = 0.064 µg L^{-1}** (for inland surface waters) and the **$AA\text{-}QS_{sw,\ eco}$ = 0.014 µg L^{-1}**(for other surface waters). However, several QSs have not been endorsed by the SCHEER or were impossible to derive. Therefore, the critical EQS must be considered as provisional.

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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 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

The SCHEER is asked to consider the two generic questions in the request, as well as the following additional points on which the Sub-Group on Review of Priority Substances (SG-R) has put a specific question

- Have the EQS been correctly and appropriately derived, in the light of the available information?
- Is the pH correction an acceptable approach for deriving the EQS for ibuprofen?
- Is the additional Assessment Factor acceptable for the EQS derivation for ibuprofen? And if this accepted in principle, is an additional AF of 5 a sufficient value?

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 several other substances and dossiers.

It is stated on the front page of the EQS dossier of ibuprofen that: "*Large parts of this dossier are based on or identical to the corresponding sections in the EQS Dossier drafted by the Swiss Centre for Applied Ecotoxicology in 2021 (Ecotoxcentre 2021).*". The proposed AA_QS in the Swiss dossier was 0.002 μgL^{-1}, based on a NOEC of 0.1 $\mu g\ L^{-1}$ (Mohd Zanuri *et al.* (2017)), however, this study did not meet the CRED validation criteria in the current dossier. The validation of the CRED criteria is beyond the scope of this mandate for the SCHEER, but a more detailed explanation of why this reference did not meet the CRED validation would be appreciated, especially since it leads to different EQS.

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

Section 7.2 Effect Data

The dossier explains that whilst several ibuprofen studies are available, the majority do not meet sufficient reliability or CRED scores. A particular difficulty working with this molecule is that bioavailability is closely linked to pH, even within the neutral range, so if this is not tightly controlled, the results can be unreliable. Only three studies in Table 7.1 have acceptable reliability scores, a study on an algae, a crustacean and one on a fish by Constantine *et al.* (2020). The fish, as a vertebrate might be assumed to be more responsive to a pharmaceutical than an algae or crustacea due to the likelihood of having receptors that resemble those in humans. The SCHEER accepts that in the case of ibuprofen, it is not currently possible to apply a probabilistic approach for the derivation of EQSs due to the lack of sufficient reliable data.

Section 7.2.1 pH correction

The proportion of the ibuprofen molecule that becomes neutral (hydrophobic) increases as the pH decreases. This is relevant in that higher cell uptake is associated with this form (Chang *et al.*, 2021). Whilst it is considered that 93% of European waterbodies are >pH 7, it is necessary that the Commission develops standards that are protective of all European waterbodies. The SCHEER, therefore, considers it appropriate that some way is found to extrapolate test data to a waterbody of a lower pH/higher risk. The dossier offers such a method in section 3.4.

Section 7.3 Acute Aquatic Ecotoxicity

The SCHEER is in agreement with the comments in the dossier on Table 7.1 and Table 15.1 that there are insufficient acute study data that may be used for a $MAC_{fw,eco}$ derivation.

Section 7.4 Chronic Aquatic Ecotoxicity

The SCHEER agrees with the dossier that the study of Constantine *et al.* (2020) is suitable and may be used in drawing up an EQS.

Section 7.5 Tentative QS_{water}

Section 7.5.2 Derivation of the AA-$QS_{freshwater,eco}$, using the deterministic approach

The study from Constantine *et al.* (2020) generated a NOEC of 55 µg L^{-1}. The study from Constantine et al. (2020) reported a mean (±SD) pH of 7.25 ± 0.25. this means that the most conservative pH is mean plus standard derivation (SD), equal to a pH of 7.5. This is correct, , so the correction factor to be used is 8, and the the SCHEER agrees with the normalised NOEC = 6.88 µg L^{-1}.

The next stage is to choose appropriate AF. The dossier recommends that given that we also have values for algae and crustacea, an AF of 10 could be used. But the dossier goes on to point out that since the Constantine *et al.* (2020) study did not review other relevant end-points like gonadal development, an additional AF of 5 is needed (giving a total AF of 50). Therefore, starting from the suggested NOEC for *Danio rerio* of 6.88µg L^{-1} (pH corrected), an **AA-$QS_{fw,eco}$** of 6.88/50 = **0.138 µg L^{-1}** (rounded to **0.14**) was derived. It is the opinion of the SCHEER that the procedure is correct.

The SCHEER agrees that not enough studies are available for applying the probabilistic approach and that the community study available is not suitable for the derivation of QS.

Section 7.5.5 Derivation of the AA-$QS_{saltwater,eco}$, using the deterministic approach

In an analogous manner, the SCHEER advises deriving an **AA-$QS_{sw,\ eco}$ = 0.014 µg L^{-1}** based on the NOEC for *D. rerio* of 6.88 µg L^{-1} (pH corrected) following an additional AF of 10.

Section 7.6 Derivation of the $QS_{sediment}$

The SCHEER agrees that as ibuprofen does not bind strongly to sediment, or that sediment dwelling organisms are more sensitive, a $QS_{sediment}$ is not necessary.

Section 7.7 Derivation of the $QS_{water,secpois}$.

Since the reported logP (logKow) > 3 and the BCF and BAF values exceed 100 L kg^{-1}, it is correct to evaluate the $QS_{biota,secpois,fw}$..

The highest BAF reported was for omnivorous fish (*Tachysurus fulvidraco* or *Pelteobagrus fulvidraco* at trophic level 3 and not 4) 113 L kg^{-1}. Because for substances with a log K_{ow} < 4.5, a default BMF of 1 is used, therefore the selected BAF multiplied by BMF yields 113 L kg^{-1}.

The lowest 28d-NOAEL (for ulcerogenicity) identified, for dogs, is 4 mg kg_{bw}^{-1} d^{-1}. Based on these data, a $QS_{biota,\ secpois}$ = 0.159 mg kg_{ww}^{-1} and a $QS_{water,\ secpois}$ = 1.41 µgL^{-1} are calculated.

As discussed above, a correction for logD at the pH of the respective exposure solution or surface water is warranted. The BAF of 113 L kg^{-1} was calculated for water samples with a pH of 8.22 ± 0.13. For *P. fulvidraco*, tolerable pH ranges of 6-7.6, 6.5-7.2 and of 7-7.8 have been reported[2].

The correction factor (CF) is assessed as follows: $CF = 10^{\Delta \log D}$ with Δ log D = log $D_{(pH\ 1)}$ - log $D_{(pH\ 2)}$ (as described in section 3.4). This would result in a CF= 21.88. In the report the correction factor is calculated as Ratio logD1/logD2 = 3.68. Therefore, the SCHEER cannot endorse the proposed $QS_{water,secpois}$ = 1.41/3.68 µg L^{-1} =0.383 µg L^{-1}.

It is the opinion of the SCHEER that the procedure is correct. However, a CF of 21.88 must be applied, leading to a **$QS_{water,secpois}$** = 1.41/21.88 µg L^{-1} =**0.064 µg L^{-1}**

Section 7.8 Bioaccumulation

The dossier gives several BCFs and BAFs, but these are not taken forward to determine a QS_{biota}. Therefore, the SCHEER is not able to advise on this section.

Section 8 Toxicity of Transformation Products

SCHEER agrees that making a general conclusion on the toxicity of ibuprofen transformation products is not possible at present due to missing information on the complex degradation pathways (11 known metabolites).

Nevertheless, based on the available evidence, SCHEER is of the opinion that for some metabolites, e.g. 4-isobutylacetophenone and 4-acetylbenzoic acid, further toxicity studies are warranted to better understand whether quality standards derived for the parent compound are sufficiently protective towards effects in aquatic ecosystems.

Section 9 Human health

A TL_{hh} has been identified, Schwab et al (2005) derived an ADI of 110 µg $kgbw^{-1}$ d^{-1}, based on human consumption data. Following the Technical Guidance for Deriving Environmental

[2] https://www.planetcatfish.com/common/species.php?species_id=457;
https://akwa-mania.mud.pl/ryby-i-rosliny/atlas-ryb/ryby-t-2/tachysurus-fulvidraco/
https://www.fischlexikon.eu/fischlexikon/fische-suchen.php?fisch_id=0000001529

Quality Standards the SCHEER a $QS_{biota\ hh}$ for fish consumption can be calculated $QS_{biota\ hh}$ = 0.2x TL_{hh} / 0.00163 = 13496.93 µg kg_{biota}^{-1} or 13.5 mg kg_{biota}^{-1}

The SCHEER notes that the health-related indicator value for drinking water proposed by the German authority (GOW) is not listed in Table 9.2. The default maximum acceptable concentration of a pharmaceutical in drinking water is 0.1 µg L^{-1} (DVGW, 2015).

4. Critical EQS

Considering the approved QSs, the critical EQSs are the **$QS_{water,secpois}$ = 0.064 µg L^{-1}** (for inland surface waters) and the **AA-$QS_{sw,\ eco}$ = 0.014 µg L^{-1}**(for other surface waters). However, several QSs have been not endorsed by the SCHEER or were impossible to derive. Therefore, the critical EQS must be considered as provisional.

5. 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
CF	Correction factor
CRED	Criteria for Reporting and Evaluating ecotoxicity Data
EQS	Environmental Quality Standards
MAC-QS	Maximum Acceptable Concentration Quality Standard
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
SSD	Species Sensitivity Distribution

6. REFERENCES

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