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COMMENTARY

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Comment on Environmental quality standards for diclofenac derived under the European Water Framework Directive: 1. Aquatic organisms

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Abstract

Leverett et al. commented on the Environmental quality standard (EQS) for diclofenac derived under the European Water Framework Directive [Leverett et al. (2021) Environ Sci Eur 33: 133 https://doi.org/10.1186/s12302-021-00574-z]. They postulated that the derivation of the EQS value for diclofenac is not conducted according to the EQS Technical Guidance, but rather using data of poor reliability and relevance. Consequently, the authors suggested using their alternative derived value instead. It is to be noted that the process for the EQS derivation for diclofenac is still ongoing and not finalized, and that as a consequence, any critical analysis is very premature. In general, within the current European Commission process, EQS values proposals are derived by expert groups led by the Joint Research Centre. In the specific case for diclofenac, Leverett et al. have also been actively involved as experts. This response to Leverett et al. (2021) aims to clarify the reasoning behind the proposal from a scientific point of view and to express our concern for the lack of transparency of their position in the statement of competing interests. Indeed, the authors did not disclose their participation in the expert group for deriving the diclofenac EQS value, nor that they have direct and indirect ties to a company that markets diclofenac in Europe, Glaxo Smith & Kline plc (GSK). This amounts to a significant conflict of interest and leads to disinformation to the reader.

Keywords: Diclofenac, Environmental quality standard, Ecotoxicity, European Water Framework Directive

Leverett et al. [1] commented on the generation of the Environmental Quality Standard (EQS) dossier for diclofenac for the European Water Framework Directive (WFD) and criticized the derived EQS value in the draft dossier. This value was derived by a subgroup of experts chaired by the Joint Research Centre (JRC) and the German Environment Agency (UBA).

Leverett et al. brought up valuable points concerning the problematics related to deriving an EQS value for diclofenac. However, in our view, the derivation of the alternative EQS, as proposed by Leverett et al. does not solve these problems in accordance with the Technical guidance document on EQS [2]. Moreover, the commentary of Leverett et al. and in particular the statement of competing interests, is in our opinion not fully transparent as it does not clearly state that all authors have direct or indirect ties to a company that markets diclofenac in

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Europe, Glaxo Smith & Kline plc (GSK). This amounts to a significant conflict of interest.

Evidently, GSK does not only submit pharmaceutical environmental risk assessments to regulatory authorities, as suggested in the competing interests, but it is also a leading company in the diclofenac market. Therefore, GSK has a clear financial interest in the outcome of the dossier.

Furthermore, we would like to note that, although the authors are heavily criticizing the diclofenac draft dossier, four of the five authors (D. Leverett, G. Merrington, M. Crane, J. Ryan) were actually participants of this expert group and therefore actively involved in generating this same draft dossier. The preparatory phase and the drafting phase of the dossier, included lengthy discussions with the mentioned authors and other experts on all details, in numerous meetings, for several months. The criticized information in the final dossier in our view merely includes the 'diverging' views of all other experts (non-GSK associated experts), while this has regrettably not been clearly indicated in the Leverett et al. paper.

As participants of that expert group and with long experience in Environmental Risk Assessments including generating EQS dossiers within the context of the WFD, the authors should know the process and the individual steps of generating such a dossier. The status of the draft diclofenac dossier is still "a work in progress", being today (December 2021) in the EU internal review process. In line with the EU-Commission strategy of full transparency, this draft version is available on the CIRCABC website [3]. So, some of the details Leverett et al. are criticizing in their comments might still be modified during the EU-Commission internal peer' review process, conducted by a panel of independent scientists via the EU's Scientific Committee on Health and Emerging Environmental Risks (SCHEER).

Leverett et al. [1] are commenting on the use of the mesocosm data of Joachim et al. [4]. They question the reliability of the mesocosm study, claiming that the evaluation criteria were not fulfilled, and also claiming that statistically significant effects were only seen at the highest concentration (stickleback data). They suggested using their Species Sensitivity Distribution (SSD) approach instead.

However, in studies with such a high variability (which is normal for mesocosm studies) the traditional "hypothesis testing" (testing for differences between mean or median values, e.g., analysis of variance), which Leverett et al. employed, has a low degree of statistical power (you need a high degree of effect to achieve statistical significance, in this case probably more than 75% effect). The result of such a statistical test is actually quite meaningless, while regression and correlation analyses are designed to analyse trend data, and thus dose–response data, and these statistical tests are far less influenced by high variability, and in general have a greater power with dose–response data. As the correlation is statistically significant at the 5% level, there is a statistically significant dose–response, and you cannot speak of there being no significant effects at the intermediate concentrations.

As laid out in detail in chapter 6.3.1.2 and Annex 2 of the draft dossier, the SSD displays a significant bimodal distribution [3]. The technical guidance document for deriving environmental quality standards (TGD-EQS) [2] requires the data to follow a distinct distribution, usually a normal distribution, if the SSD is used to derive the EQS. In case such a distribution is not shown for the whole data set, it is recommended to do an SSD for the more sensitive taxonomic groups. If the data from this second SSD are normally distributed, the resulting HC5 can be used for EQS derivation (TGD, chapter 3.3.1.2, page 44):

> *"If the data do not fit any distribution, the left tail of the distribution (the lowest effect concentrations) should be analysed more carefully. If a subgroup of species is particularly sensitive and, if there are sufficient data, an SSD may be constructed using only this subgroup. However, this should be underpinned if possible by some mechanistic explanation, e.g., high sensitivity of certain species to this particular chemical. The SSD method should not be used in cases where there is a poor data fit to all available distributions."*

In contrast to, e.g., substances with an estrogenic mode of action like estradiol and ethinylestradiol, for diclofenac there are no clear taxonomic related differences found in the distribution of the SSD. This is highly visible through the data collated and analysed by the expert group and documented in the draft EQS dossier. For example, two autotrophic species (*Dunaliella tertiolecta* and *Desmodesmus subspicatus)* are on the higher end of the distribution while duckweed (*Lemna minor)* is shown to be the second most sensitive species. Moreover, fish toxicity data ranged from 3.5 µg/L for *Salmo trutta* up to 674 µg/L for *Cyprinus carpio*.

Consequently, no specific sensitive species group could be determined and thus, there were no ecological or taxonomic reasons to use one part of the SSD only and exclude other studies, i.e., no specific sensitive species group could be established.

These results suggest the SSD approach may not be applicable in the case of diclofenac. No mechanistic explanation for a sensitive subgroup could be identified. This is the main and scientifically sound reason why, in

line with the TGD [2], the expert group suggested not to use the SSD at all for setting the EQS.

In contrast, Leverett et al. [1] wrote: "*However, it is debatable whether this SSD is truly bimodal since the 40 and 120 µg L^{-1} data points bridge the gap between these lower (sensitive) and upper (insensitive) portions of the SSD curve.*"

Later in the text the authors are suggesting to just use the sensitive part of the SSD, without any biological explanation, but citing the TGD "*not all data have equal influence on the derivation, with so-called 'critical' data strongly influencing the resultant EQS as stated in EU guidance document*" [2]. Here, the authors are omitting parts of the citation. In the same paragraph (chapter 2.6.3, p. 27–28 the TGD states: "*If a species sensitivity modelling approach is adopted, a distinction between critical and supporting data does not apply. This is because all the data are used in the model extrapolation and so, all the data can be regarded as critical (as long as they are reliable and relevant).*"

In the second part of their commentary Leverett et al. [1] are commenting on the use and the interpretation of the monitoring data, generated and provided by the individual member states. Here the authors are however making some crucial but scientifically incorrect simplifications:

> Leverett et al. [1] developed the indicative compliance assessment on a basis of the country level (mean of 90th percentiles of individual countries) instead of at the level of monitoring sites as stipulated in the Environmental Quality Standards (EQS) Directive 2008/105/EC [5].
>
> In the commentary, the 90th percentiles (as well as the other statistical parameters) are estimated only by a substitution approach, just setting the data, which are less than the limit of quantification as half of the limit of quantification value. This is in contrast to an earlier paper of the same authors [6], where this substitution is postulated as a bias-prone method that should not be used in risk assessment. In addition, this paper is lacking information about confidence intervals of the derived statistics, thus the possible range of statistical parameters is unknown which reduces the robustness of their results.
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> In the collected dataset for European surface waters, France is overrepresented since it holds about 80% of all reported samples. Although this is mentioned in the text, the paper does not consider a data scenario "evaluation without the most data-rich country" in order to assess what impact on the final results this country would have. Instead, four countries [Austria, Belgium (Flanders), Germany and Hungary] which have shown many exceedances compared to the EQS were eliminated, and in a second step specifically analysed.
>
> Leverett et al. said when commented the indicative compliance assessment for diclofenac in European surface waters that they calculated (unweighted) mean of the 90th (P90) and 95th (P95) percentiles from each individual county. However, the provided values (P90 = 0.090 µg L^{-1} and P95 = 0.157 µg L^{-1}) represent the weighted means of P90 and P95 (not unweighted ones) estimated considering all reporting countries. In this case, the correct unweighted means are P90 = 0.144 µg L^{-1} and P95 = 0.22 µg L^{-1}. In addition, our calculations using the same data showed that the omitting of data from France would approximately double the weighted means of percentiles (P90 = 0.19 µg L^{-1} and P95 = 0.313 µg L^{-1}).The paper evaluates the risk mainly by considering weighted and unweighted means of 90th percentiles of measured concentrations from the participating countries. The rationale of this choice is not explained or commented upon. The authors do not explain either, why higher percentiles, for instance 95th, are not taken into consideration. Indeed, the weighted mean of the 95th percentiles of reporting countries is 0.157 µg/L which exceeds both tentative Annual Average (AA)-EQS (0.126 µg/L as derived in the paper as well as the provisional one of 0.04 µg/L according to the EC draft dossier). Actually, this result shows and confirms an environmental risk of diclofenac in EU watersheds.

Conclusion

We agree that regulatory decisions and processes should be challenged in scientific articles, and this clearly includes the process of deriving EQS values. But we disagree with using a scientific journal to claim such a disagreement during the review process of a dossier for an EQS derivation, especially as the authors neither disclose their participation in the expert group nor the company's financial interest in the EQS setting.

In our opinion, Leverett et al. aim to use this journal to disseminate their view including answers to the points raised in their article. The goal of this paper s seems to be to provide a misinformation on the ongoing process for the diclofenac EQS derivation in particular, and the European EQS derivation process in general.

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Authors' contributions
TL and GM drafted the first version, LÄ, MC, HC, AJ, MJ, VJ, DM, GS, RT, EV made substantial contributions to the conception, analysis, and interpretation of data and assisted in drafting the work. Each author approved the submitted version (and any substantially modified version that involves the author's contribution to the study) and agrees both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors read and approved the final manuscript.

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All authors were and still are invited participants of the expert group for deriving an EQS value for diclofenac. This group is led by the Teresa Lettieri (JRC) and Gerd Maack (UBA).

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