



COMMENTARY

Open Access



Comment on Environmental quality standards for diclofenac derived under the European Water Framework Directive: 1. Aquatic organisms (Leverett et al. in *Environmental Sciences Europe* 2021; 33: 133)

Gerd Maack^{1*}, Lauri Äystö², Mario Carere³, Henning Clausen⁴, Alice James⁵, Marion Junghans⁶, Ville Junttila², Juliane Hollender⁷ , Dimitar Marinov⁸, Gerard Stroomberg⁹, Rita Triebkorn¹⁰, Eric Verbruggen¹¹ and Teresa Lettieri^{8*} 

Abstract

Leverett et al. commented on the Environmental quality standard (EQS) for diclofenac derived under the European Water Framework Directive (Leverett et al. *Environ Sci Eur* 33: 133, 2021 <https://doi.org/10.1186/s12302-021-00574-z>). They postulated that the derived EQS value for diclofenac is not conducted according to the EQS Technical Guidance but rather using data of poor quality and relevance. Consequently, the authors suggested to use 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 value proposals are derived by expert groups led by the Joint Research Centre. In the specific case for diclofenac, Leverett and co-authors have also been actively involved as experts. This response to Leverett et al. (*Environ Sci Eur* 33:133, 2021) aims to clarify the reasoning-behind the proposal from a scientific point of view.

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 sub-group 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].

As stated in the conflict of interest one author (Jim Ryan) works for a company Glaxo Smith & Kline plc (GSK) that produces diclofenac, sells products containing diclofenac, and submits environmental risk assessments for pharmaceuticals to regulatory authorities. In fact, GSK a leading company in the diclofenac market.

Furthermore, we would like to note that, although the authors are heavily criticizing the diclofenac draft dossier,

*Correspondence: gerd.maack@uba.de; Teresa.LETTIERI@ec.europa.eu

¹ Environmental Risk Assessment of Pharmaceuticals, German Environment Agency (UBA), Wörlitzer Platz 1, 06844 Dessau-Roßlau, Germany

⁸ DG Joint Research Centre, European Commission, Directorate D-Sustainable Resources, Unit D.02 Water and Marine Resources TP 121, Via Enrico Fermi, 2749, I-21027 Ispra, VA, Italy
Full list of author information is available at the end of the article

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 same dossier, included lengthy discussions with the mentioned authors and with other experts on all details, in numerous meetings, for several months. The criticised information in the final dossier in our view merely includes the ‘diverging’ views of other experts (non-GSK associated experts), while this has regrettably not been clearly indicated in the Leverett et al.’s 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 “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 before the internal review is available on the CIRCABC website [2]. Therefore, some of the details Leverett et al. are criticizing in their comments might still be modified during this internal review process. In addition, publicly available data that are still “work in progress” can differ from the ‘final’ dossier which is not available yet, especially because the dossier is currently still being ‘peer’ reviewed by a panel of independent scientists via the EU’s Scientific Committee on Health and Emerging Environmental Risks (SCHEER).

Leverett et al. [5] are commenting on the use of the mesocosm data of Joachim et al. [4].

They question the validity of the mesocosm study, claiming that the reliability criteria were not fulfilled, and also claiming that statistically significant effects were only seen at the highest concentration (stickleback data). They suggested to use their Species Sensitivity Distribution (SSD) approach instead. However, this topic was discussed in all details during the sub group meetings. The majority of the experts regarded the mesocosm study as reliable and useful, and concerning the lack of statistical significance of effects at lower concentrations, it was pointed out that there was a statistically significant correlation between concentration and effect. In studies with such a high variability (which is normal for mesocosm studies) the traditional “hypothesis testing”, which Leverett et al. employed, has a low degree of statistical power, and is actually quite meaningless.

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 [2]. The technical guidance document for deriving environmental quality standards (TGD-EQS) [1] 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 given 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 analysed 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, it was considered that there were no ecological or taxonomic reason 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 that 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 [1], the expert group suggested not to use the SSD at all for setting the EQS.

In contrast, Leverett et al. [5] 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”* [1]. Here, the authors are obviously 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. [5] 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:

- They 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 Directive 2008/105/EC.
- In this paper, 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 Merrington et al. [6], where the same authors postulate the substitution 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.
- In the collected dataset for European surface waters, one of the participating countries is overrepresented since it holds about 80% of all reported samples. Although this is mentioned in the text, this paper does not consider a data scenario "evaluation without the most data-rich country" to assess what impact on the final results this country would have. Instead, four countries which have shown many exceedances comparing to the EQS were eliminated, and in a second step specifically analysed.
- This paper evaluates the risk mainly by considering weighted and unweighted means of 90th percentiles of measured concentrations in 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 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 a risk of diclofenac in EU watersheds.

Conclusion

We agree that regulatory decisions and processes should be challenged in scientific articles, but we completely disagree with using a scientific journal to claim such a disagreement *during the review process* of a dossier for an EQS derivation.

Acknowledgements

Not applicable.

Author 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.

Authors information

Lauri Äystö is a researcher at the Finnish Environment Institute (SYKE) Contaminants unit, and a PhD student at the University of Helsinki. In his work, he focuses on the emissions, occurrence, and risks of pharmaceuticals in the environment.

Mario Carere is a senior researcher at the Ecosystems and Health Unit of the Italian Institute of Health. He is co-chair of the WG Chemicals of the Water Framework Directive. He has a long science-policy experience in environmental and human health risk assessment, application of effect-based methods and derivation of environmental quality standards.

Henning Clausen is an ecotoxicologist who worked for more than 30 years with environmental hazard and risk assessment of chemicals at the Danish Environmental Protection Agency, including derivation of environmental quality standards. After retirement, he has been a consultant for the Danish EPA on hazard and risk assessment.

Alice James is a senior scientist at the French National Institute for Industrial Environment and Risks (INERIS), Environmental characterisation and impacts on human and biodiversity Department. One of her main assignments are derivation of Environmental Quality Standards for the French Ministry in charge of the environment and environmental risk assessment of chemicals. Marion Junghans is a senior scientist and heads the risk assessment group at the Swiss Centre for Applied Ecotoxicology. The Ecotoxcentre is developing and proposing environmental quality criteria for surface waters to the Swiss Federal Office for the Environment for potential implementation under the Swiss Water Protection Ordinance.

Ville Junttila is a researcher at the Finnish environment institute (SYKE) and a PhD student at the University of Helsinki. He works at several research projects funded by the Ministry of the Environment and Ministry for Foreign Affairs of Finland.

Juliane Hollender is a senior scientist and head of the department Environmental Chemistry at the Swiss Federal Institute of Aquatic Science and Technology (Eawag) as well as an adjunct professor at ETH Zurich. Due to her expertise in exposure and bioaccumulation assessment, she has been part of the European expert group for deriving the diclofenac EQS value.

Teresa Lettieri (European Commission, DG Joint Research Centre (JRC) is leader of the molecular ecotoxicology activities, risk assessment of emerging pollutants in water and coordinator of the prioritisation process and Watch List program under the European Water Framework Directive.

Gerd Maack is a senior scientist at the German Environment Agency (UBA), Department of Pharmaceuticals. He is assessing the Environmental Risk Assessment of Human and Veterinary Medicinal Products. He also is a scientific advisor for the European Medicine Agency (EMA) and for the German Ministry of Environment (BMU).

Dimitar Marinov works for the JRC. He is responsible for the collection and processing of data for measured environmental concentrations of chemicals, check of data quality, statistical analyses and risk assessments.

Gerard Stroomberg is director of RIWA-Rijn, the association of drinking water suppliers in the Netherlands that are dependent on the river Rhine as their source for clean and wholesome drinking water. RIWA-Rijn represents the interests of its members in various national and international working groups, such as are hosted by the Dutch Ministry of Infrastructure and Water Management, the International Commission for the Protection of the Rhine and the European Commission. RIWA-Rijn is member of the International Association of Waterworks in the Rhine Catchment Area (IAWR) and signatory party to the European River Memorandum for Quality Assurance of Drinking Water Production (ERM 2020).

Rita Triebkornis a professor and group leader at the Institute of Evolution and Ecology, University of Tübingen, and head of the Steinbeis Transfer-Center for Ecotoxicology and Ecophysiology, Rottenburg. She has more than thirty years of experience in ecotoxicological research.

Eric Verbruggen is a senior risk assessor at the Dutch National Institute for Public Health and the Environment. He is involved in quality standard setting on national and international level (water and soil) and on REACH tasks primarily related to PBT (member of ECHA PBT Expert Group) and Substance Evaluations.

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).

Funding

Not applicable.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

Author details

¹Environmental Risk Assessment of Pharmaceuticals, German Environment Agency (UBA), Wörlitzer Platz 1, 06844 Dessau-Roßlau, Germany. ²Finnish Environment Institute (SYKE), Latokartanonkaari 11, 00790 Helsinki, Finland. ³Department Environment and Health, Italian Institute of Health, Viale Regina Elena, 299, 00161 Rome, Italy. ⁴Danish Environmental Protection Agency (Retired), Kongemarksvej 22, 2700 Brønshøj, Denmark. ⁵Expertise en toxicologie/écotoxicologie des substances chimiques (ETES), French National Institute for Industrial Environment and Risks INERIS, Parc ALATA, BP2, 60550 Verneuil-en-Halatte, France. ⁶Swiss Centre for Applied Ecotoxicology, Überlandstrasse 133, 8600 Dübendorf, Switzerland. ⁷Swiss Federal Institute of Aquatic Science and Technology, Überlandstr. 133, 8600 Dübendorf, Switzerland. ⁸DG Joint Research Centre, European Commission, Directorate D-Sustainable Resources, Unit D.02 Water and Marine Resources TP 121, Via Enrico Fermi, 2749, I-21027 Ispra, VA, Italy. ⁹Association of River Water Companies, Section Rhine (RIWA-Rijn), Groenendael 6, 3439 LV Nieuwegein, The Netherlands. ¹⁰Institute of Evolution and Ecology, University of Tübingen and Steinbeis Transfer-Center for Ecotoxicology and Ecophysiology, Rottenburg, Auf Der Morgenstelle 5, 72076 Tübingen, Germany. ¹¹National Institute for Public Health and the Environment (RIVM), P.O. Box 1, 3720 BA Bilthoven, The Netherlands.

Received: 24 January 2022 Accepted: 19 February 2022

Published online: 12 March 2022

References

1. European Commission (EC) (2018) Revised Technical Guidance for deriving Environmental Quality Standards. Common Implementation Strategy

for the Water Framework Directive Guidance Document No. 27. European Commission. <https://circabc.europa.eu/ui/group/9ab5926d-bed4-4322-9aa7-9964bbe8312d/library/ba6810cd-e611-4f72-9902-f0d8867a2a6b/details>

- European Commission (EC) (2021) Draft EQS Datasheet: Diclofenac. <https://circabc.europa.eu/ui/group/9ab5926d-bed4-4322-9aa7-9964bbe8312d/library/696bd6ba-0a50-4d6c-bbfd-d59b1c848c36>.
- Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008L0105&from=EN>.
- Joachim S, Beaudouin R, Daniele G, Geffard A, Bado-Nilles A, Tebby C, Palluel O, Dedourge-Geffard O, Fieuc M, Bonnard M, Palos-Ladeirod M, Turisa C, Vulliet E, David V, Baudoin P, James A, Andres S, Porcher JM (2021) Effects of diclofenac on sentinel species and aquatic communities in semi-natural conditions. *Ecotoxicol Environ Saf* 211:111812. <https://doi.org/10.1016/j.ecoenv.2020.110731>
- Leverett D, Merrington G, Crane M, Ryan J, Wilson I (2021) Environmental quality standards for diclofenac derived under the European Water Framework Directive: 1. Aquatic organisms. *Environ Sci Eur* 33:133. <https://doi.org/10.1186/s12302-021-00574-z>
- Merrington G, Peters A, Wilson I, Gardner M, Rutherford S, Baken S, Schlegel C, Cooper C, Mertens J, Adams W, Van de Merck L, van Nes J, Leondina LD, Ryan J (2021) Using exposure data to identify priority substances under the European Water Framework Directive: the quest to reflect uncertainties. *Environ Toxicol Chem* 40(5):1237–1238. <https://doi.org/10.1002/etc.4987>

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen[®] journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)