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Improvements in estimating bioaccumulation metrics in the light of toxicokinetics models and Bayesian inference

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abstract

The surveillance of chemical substances in the scope of Environmental Risk Assessment (ERA) is classically performed through bio-assays from which data are collected and then modelled. Some statistical analysis base on the fitting of toxicokinetic (TK) models to assess the bioaccumulative capacity of chemical substances via the estimation of bioaccumulation metrics as required by regulatory documents. Given that bio-assays are particularly expensive and time consuming, it is of crucial importance to deeply benefit from all information contained in the data. By revisiting the calculation of bioaccumulation metrics under a Bayesian framework, this paper presents improvements in the classification of the bioaccumulative capacity of chemical substances. A meta-analysis of a data-rich TK database was performed, considering the uncertainties around the bioaccumulation metrics. The subsequent results appeared sufficiently statistically robust to propose the replacement of the single median estimate to decide of the class to which assign a chemical substance. The main recommendation is to use the 75^{th} percentile of the uncertainty interval of the bioaccumulation metrics, which revealed a better criterion to classify a chemical substance, and in the same way as the conventional method in 90% of cases.

Keywords: Environmental Risk Assessment, classification of chemical substances, REACH regulation, accumulation-depuration test.

1 Introduction

Chemical substances, present in the environment as a result of human activities, are of extreme concern due to their persistence, to their capacity in accumulating within non-target living organisms and to their potential toxicity on the different levels of biological organization all along trophic chains (Cousins et al., 2019; Popek, 2018). In particular, this reveals crucial to bring reliable and precise information on the bioaccumulative capacity of the different chemical substances, on what depend the concentrations internalized by organisms almost exclusively. This stage then conditions the way in which relevant links can be established between the exposure concentrations and the likely damages on life-history traits (Arnot and Gobas, 2006; Chojnacka and Mikulewicz, 2014; Armitage et al., 2021).

In Europe, chemical substances are governed by the REACH regulation, adopted by the European Union to improve the protection of human health and the environment from the risks that can be raised by chemical substances (European Commission, 2006). In principle, REACH applies to all chemical substances, also stipulating the need to reduce animal testing. To comply with the regulation, manufacturers must identify and manage the risks linked to the chemical substances in demonstrating that they can be safely used. For example, in order to evaluate the bioaccumulative capacity of chemical substances, produced or imported above 100 tonnes per year, the REACH regulation requires the calculation of bioaccumulation metrics. According to Ratier et al. (2021b), we use the generic expression “bioaccumulation metrics” to denote either bio-concentration factors (BCF) used when exposure is via water, biota-sediment accumulation factors (BSAF) when exposure is via sediment or biomagnification factors (BMF) when exposure is via food. For substances produced or imported between 10 and 100 tonnes per year, bioaccumulation

metrics are not mandatory but still required to classify chemical substances as persistent, bioaccumulative and toxic (abbreviated PBT) or very persistent and very bioaccumulative (abbreviated vPvB). Most of European countries classify substances as bioaccumulative (abbreviated "B") if the bioaccumulation metric is in $[2000; 5000[$, or very bioaccumulative (abbreviated "vB") if it is > 5000 (European Commission, 2006). Other regulations around the world (Saito et al., 2011; Government of Canada, 1999; Agency, 1979) classify as "B" a chemical substance with a bioaccumulation metric ranging in $[1000; 5000[$. Chemical substances with a bioaccumulation metric in $]1000; 2000[$ are always classified as low bioaccumulative (abbreviated as "ℓB"). These classifications are summarized in Wassenaar et al. (2020) and by Hartmann et al. (2014).

Bioaccumulation metrics are calculated from toxicokinetic (TK) parameter estimates by fitting a TK model (usually a one-compartment model) to experimental data collected during bioaccumulation tests (*e.g.*, OECD (2008, 2012)). Bioaccumulation tests provide internal concentration measurements from two-phase experiments: a first phase (the "accumulation" phase) during which organisms are exposed via one or several uptake route(s) (water, pore water, sediment and/or food) to a given chemical substance, kept constant over time; a second phase (the "depuration" phase) during which organisms are transferred into a clean medium where elimination processes take place. The TK model is expected to account for all uptake routes and elimination processes (including excretion, dilution by growth and/or metabolization) to better describe the overall kinetics in terms of internal concentrations. From TK parameter estimates (namely, uptake and elimination rates), two types of bioaccumulation metrics can be calculated: the "kinetic" bioaccumulation metric, as the ratio between uptake and elimination rates; and the "steady-state" bioaccumulation metric as the ratio of the internal concentration at steady state and the constant exposure concentration; the steady state is defined as

the plateau concentration that is expected at the end of the accumulation phase. In theory, the "steady-state" bioaccumulation metric should be calculated only if the internal concentrations measured at the last three time points of the accumulation phase are not significantly different.

In addition to the experimental procedure of bioaccumulation tests, the OECD guidelines also explain how to obtain bioaccumulation metrics depending on the exposure routes that have been considered within the experiments. If a one-compartment TK model is often sufficient. So, in case the goodness of fit is poor this may be an indication that first order kinetics does not apply suggesting that a more complex model should be employed. For example, one of the most common complexities to account for is fish growth during the bioaccumulation test (OECD, 2012). Surprisingly, in such a case, guidelines only recommend to seek advice from bio-statistician and/or pharmacokineticist experts. In addition, very few tools exist to easily perform TK analyses. To name but a few, there are the Excel macro by Gobas et al. (2020), the "bcmfR" package (OECD, 2012) and the free open-source MOSAIC$_{bioacc}$ web service (`http://umr5558-shiny.univ-lyon1.fr/mosaic-bioacc/`) that has been recently updated (Ratier et al., 2021b; Charles et al., 2021a). Only MOSAIC$_{bioacc}$ is entirely generic whatever the species-compound combination of interest, allowing to account for different exposure routes and several elimination processes simultaneously, automatically adapting the fitted TK model according to the input experimental data. It provides all possible bioaccumulation metrics accordingly, namely BCF, BSAF and/or BMF.

Recently, the European Food Safety Authority (EFSA) strongly advocated the need to associate uncertainties with model parameter estimates (EFSA Scientific Committee, 2018) in general, emphasizing this need for toxicity indicators in particular (Ockleford et al., 2018). This requirement is complementary to the previous regulation with regard to the bioaccumulation metrics. Indeed,

for the authorisation dossiers of active chemical substances, the current regulatory document only ask for a single mean or a median value as bioaccumulation metrics (European Commission, 2013). Such a practice is still common today, probably because of a lack of efficient and easy tools to handle computer resources, specifically designed to automatically provide uncertainties on any model output. However, recent recommendations have clearly been established when using toxicokinetic-toxicodynamic (TKTD) models (Baudrot and Charles, 2019), while Charles et al. (2021b) highlighted how critical it is to take uncertainty into account when assessing the toxicity of a chemical substance to a range of non-target terrestrial plants thus revisiting the species sensitivity distribution (SSD) approach.

Today, when bioaccumulation metrics need to be estimated, MOSAIC$_{bioacc}$ is one of the only tools in support of a facilitated in-depth quantification of the uncertainties; on the contrary, Gobas et al. (2020) tool only gives a standard deviation. While available on-line since May 2020, the number of users of MOSAIC$_{bioacc}$ is continuously growing all over the world, whether they are from academia, regulatory bodies or industry (380 recordings these last 6 months). A publicly available database accompanies the MOSAIC$_{bioacc}$ services (`http://umr5558-shiny.univ-lyon1.fr/mosaic-bioacc/data/database/index_readme.html`), with more than 200 accumulation-depuration data sets collected within published scientific papers (Ratier and Charles, 2021). All data sets are automatically analyzed with MOSAIC$_{bioacc}$, full analysis reports being made available via the database directly. This database is dynamically supplemented as new data sets are retrieved from the recent scientific literature, or directly deposited by researchers upon request.

The aim of the present paper is to propose improvements in the estimation of bioaccumulation metrics in association with the quantification of their uncertainty with the perspective to reinforce the statistical foundations leading

to the classification of chemical substances as (low, medium or very) bioaccumulative or not. To this end, we first present the last updates brought to MOSAIC$_{bioacc}$, especially an innovative prediction device that can be specifically used in designing new experiments in full respect of the 3R principles (Replacement, Reduction and Refinement) ensuring animal welfare and quality of science (Prescott and Lidster, 2017). Then, the added value of accounting for uncertainty of bioaccumulation metrics is underlined through a meta-analysis of the TK database associated with MOSAIC$_{bioacc}$. Finally, we demonstrate how influential may be the consideration of uncertainty when classifying chemical substances according to the current regulatory intervals into which the bioaccumulation metric estimates fall. We conclude with a revisited workflow to improve environmental risk assessment if it would be adopted by regulatory bodies.

2 Calculations and predictions of bioaccumulative capacity

This section gives a brief overview of the different features of MOSAIC$_{bioacc}$. A focus is first made on the calculation of bioaccumulation metrics. Then the new prediction tool is introduced, to close with illustrative case studies.

2.1 Calculations of bioaccumulation metrics

Recent updates have been brought to the MOSAIC$_{bioacc}$ web application to increase the speed of calculations and improve titse user-friendliness. Above all, a new R-package is today available on the official CRAN web site (`https://CRAN.R-project.org/package=rbioacc`) that allows to similarly perform all MOSAIC$_{bioacc}$ calculations and graphs directly in the R software with ready-to-use dedicated functions (Ratier et al., 2021a). The new version of MOSAIC$_{bioacc}$ has entirely been rewritten to reduce the length of the source

code and take advantage of this new package. Above all, MOSAIC$_{bioacc}$ is now based on a tabbed presentation that clarifies and facilitates browsing from one step to the next. A special tab gives all bioaccumulation metrics, appropriately calculated according to the input observed data that the user has uploaded. By default, the kinetics BCF, BSAF or BMF values are delivered, displayed via their entire posterior probability distribution then summarized with their median (that is the 50% quantile) and their 95% uncertainty interval (bounded by the 2.5 and 97.5% quantiles). In addition, users can ask for the steady-state corresponding bioaccumulation metrics if they consider it relevant according to the duration of the accumulation phase, and the fact of having actually reached the plateau.

2.2 Prediction of bioaccumulation matrics to optimize experiments

A new prediction tab have been added to MOSAIC$_{bioacc}$ that allows interactive simulations of a TK model under a constant or a time-variable exposure profile. The main aim of this prediction tool is to assist experimenters in optimizing the design of new experiments, based on previous TK analyses. Indeed, when studying a new chemical substance and/or a new species, when studying a new chemical substance and/or a new species, some information needed to be known in advance in full respect of scientific ethic in terms of experiment on living organisms and chemical use and recycling. For example, the exposure concentration, the duration of the accumulation and the depuration phases as well as the number of time points at which internal concentrations should be primarily measured need to be defined in advance. Then, based on previous TK analyses for given close species/compound combinations, TK parameter estimates can serve to simulate what could be expected when planing additional time points and/or extending the accumulation phase for example.

Above all, benefiting of the Bayesian framework, the uncertainty around parameter estimates can be propagated towards predictions and any function of the parameters (Baudrot and Charles, 2019), in a way that is particularly useful when environmentally realistic exposure scenarios have to be run in numbers.

2.3 Illustrations with case studies

We provide a collection of case studies as supplementary information (SI, see the .pdf file) to illustrate various situations where the prediction tool can be helpful:

Case study 1 Plan an experiment for an already studied species exposed to a different but chemically similar compound (*i.e.*, with a mode of action expected to be close), without accounting for the parameter uncertainty;

Case study 2 Compare several species exposed to a same chemical substance accounting for the uncertainty around parameter estimates coming from a previous TK analysis conducted on a species phylogenetically (or taxonomically) close to the new set of interest. In such a case, the user will need to enter the required input information but also a tabular file with the joint posterior distribution of the parameters, either coming from a previous MOSAIC$_{bioacc}$ TK analysis or a home-made TK implementation.

Case study 3 A prediction for a same species/compound combination but for different exposure scenarios for which the user may have observed data to which simulations can be compared as a validation step of the exploited TK model.

3 Matter of uncertainty in estimating bioaccumulation metrics

Regarding accumulation-depuration data, one output of great interest is the bioaccumulative capacity of a chemical substance which is assessed through the appropriate bioaccumulation metrics according to the exposure route(s) (either the BCF, the BSAF and/or the BMF). So, benefiting of the probability distributions of these metrics (coming from the propagation of the parameter uncertainty) is crucial to catch their precision. This latter may indeed influence the classification of the substance as bioaccumulative or not, and if bioaccumulative, influence the choice between "B" or "vB" categories. In order to illustrate this critical issue for ERA, we present below a meta-analysis of the TK database associated to MOSAIC$_{bioacc}$ (Ratier and Charles, 2021).

3.1 The accumulation-depuration TK database

The TK database currently contains 211 accumulation-depuration data sets collected from a literature review and corresponding to a total of 56 studies. The 211 data sets encompass 52 genus, 124 chemical substances, three different exposure routes (water being the main one, sediment and food), 34 data sets with also biotransformation data (that is metabolization data). Figure 1 shows several tree maps performed with the `treemap` R-package (Tennekes, 2017) allowing to visualise the proportion of each chemical category (Figure 1-a) and each genus (Figure 1-b) among the 211 data sets. Pesticides and hydrocarbons are the most represented chemical substances within the TK database, what can be explained by the predominance of data sets on freshwater invertebrates and fish. *Gammarus* and *Daphnia* are the most represented genus, probably due to less ethic exigence with them, while fish studies are rarer. *Gammarus* and *Daphnia* are also the genus for which the most biotransformation data are available.

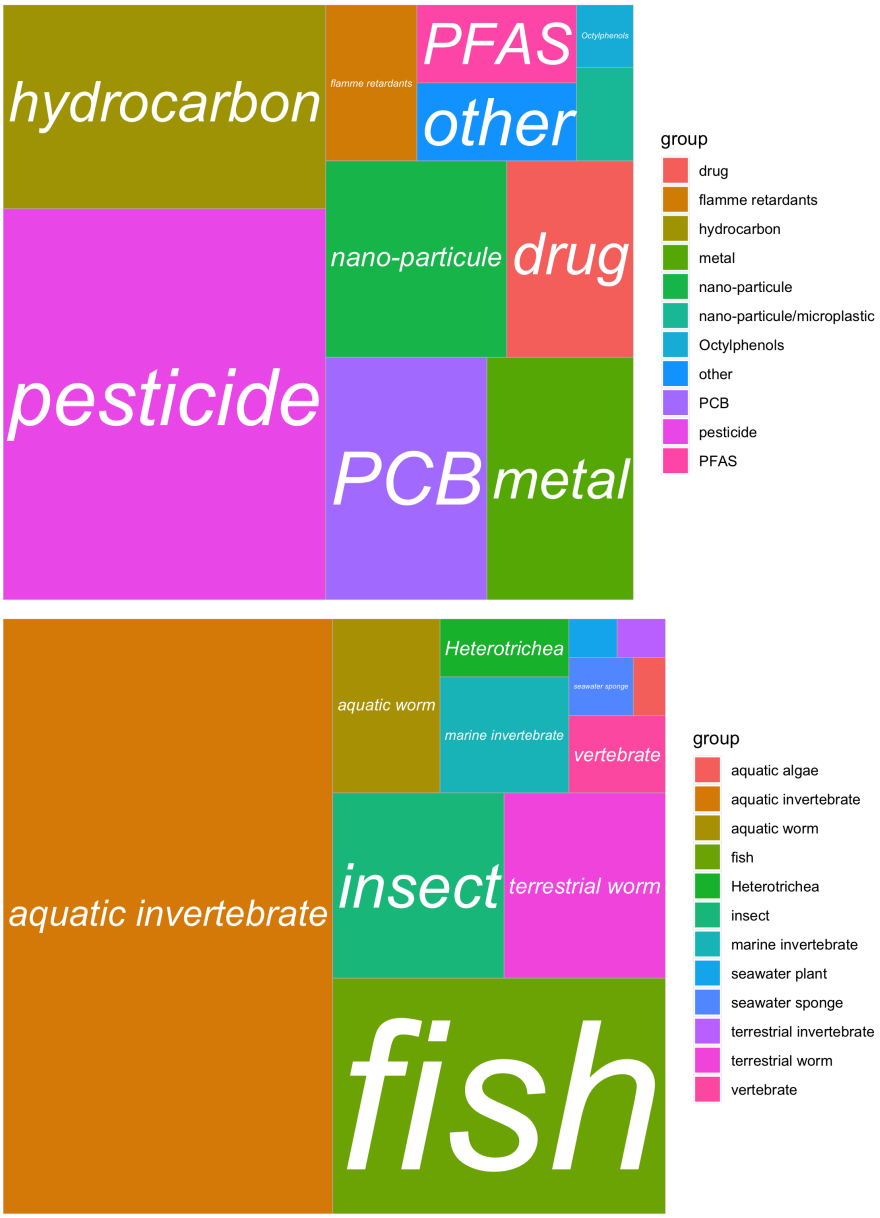

Fig. 1 Tree maps of chemical categories (upper panel) and genus categories (lower panel) available in the TK database available at `http://lbbe-shiny.univ-lyon1.fr/mosaic-bioacc/data/database/TK_database.html`.

The 211 data sets of the TK database were fully analysed with MOSAIC$_{bioacc}$. Corresponding reports are available from the database itself, as well as references from which data have been extracted. From these analyses, we conducted a meta-analysis of the bioaccumulation metrics to specifically illustrate how much accounting for uncertainty matters when characterizing the bioaccumulation capacities of chemical substances.

3.2 Meta-analysis of the TK database

Even if not required within regulatory documents, associate the uncertainty to a bioaccumulation metric is of crucial importance (Wassenaar et al., 2020). Among the 211 data sets, a total of 137 corresponds to an exposure via water for which the MOSAIC$_{bioacc}$ analysis then provides a BCF probability distribution. Based on the median and the 95% uncertainty interval of these BCF estimates (Figure 2), aquatic invertebrates have the highest values, when predominantly exposed to pesticides or metals, among which the genus *Gammarus* has the most BCF estimates greater than 5000, classifying the corresponding chemical substances as "vB". The SI (see the .html file) provides an additional figure with all the 211 estimated bioaccumulation metrics, without distinguishing BCF from BSAF and BMF estimates. Note that from this Figure, we would have concluded to similar trends. On the other hand, based on the median of the BCF estimates as required by the regulation, only 22.7% of the BCF values classify chemical substances as "B", that is with BCF medians higher than 1000. Nevertheless, as a matter of fact, this classification does not account for the precision of the BCF estimates. Hence, this raises the question of using another criterion to decide whether a chemical substance is bioaccumulative or not, and at which bioaccumulative capacity.

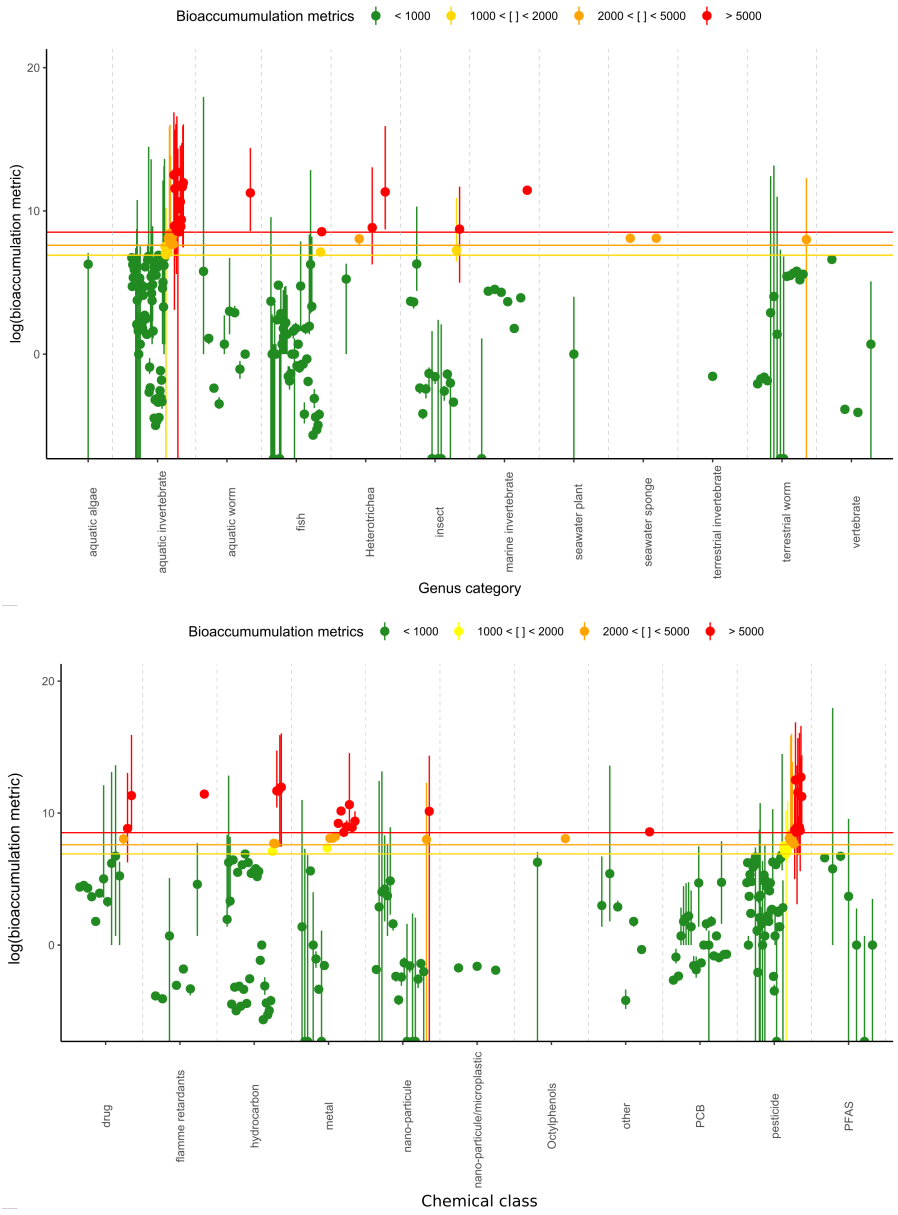

Fig. 2 Bioaccumulation metrics (in $\log_{10}$ scale) according to genus (upper panel) and chemical (lower panel) categories. Dots represent medians of the bioaccumulation metrics, while vertical segments represent the associated 95% uncertainty intervals. Horizontal lines delineate regulatory threshold values used in the regulation (1000, 2000 and 5000, respectively) to classify chemical substances according to their bioaccumulative capacity. Bioaccumulation metrics are colored accordingly: in green when the metric is < 1000; in yellow if the metric is in $[1000; 2000[$; in orange if the metric is in $[2000; 5000[$; in red if the metric is > 5000.

3.3 Towards improvements in ERA

Accounting for the precision of the bioaccumulation estimates relies on the use of their probability distribution, that can be brought into play to define a new decision criterion for the classification of chemical substances.

Instead of the median only, we first envisaged to consider the upper bound of the uncertainty interval around the bioaccumulation metric estimates, that is the 97.5% quantiles of their posterior probability distributions (referred as Q97.5 in Table 1). This raised the question of an overestimation of the bioaccumulative capacity of the chemical substances. Indeed, the number of BCF values doubled from 22 to 45 in the "vB" category (Table 1). Such a criterion would classify 36.5% of the chemical substances as bioaccumulative ($n = 77$), against only 22.7% ($n = 48$) with the usual criterion based on the median estimate (referred as Q50 in Table 1). In terms of safety prediction, this could be acceptable but still based on a biased interpretation of the bioaccumulative capacity.

Table 1 Number of chemical substances in each bioaccumulative capacity class according to the three decision criteria built on the 50%, the 75% or the 97.5% quantiles of the posterior probability distributions of the bioaccumulation metric estimates: Q50, Q75 and Q97.5, respectively. Abbreviations ℓB stands for low bioaccumulative, B for bioaccumulative and vB for very bioaccumulative, respectively.

Criterion	ℓB ($BCF \in [1000; 2000[$)	B ($BCF \in [2000; 5000[$)	vB ($BCF > 5000$)
Q50	10	16	22
Q75	11	20	30
Q97.5	10	22	45

Again in the perspective of exploiting the uncertainty on bioaccumulation metric estimates to build a new classification criterion of chemical substances,

we compared the use of the 75% quantile (referred as Q75 in Table 1) to the use of the usual Q50 or the previous Q97.5, as an alternative compromise. As illustrated on Figure 3, concerning the species *Daphnia magna* exposed to phenanthrene (Wang et al., 2021), the Q50 classifies as "nB" ($BCF < 1000$), while both the Q75 and the Q97.5 criteria classify it as "B" ($BCF > 1000$). This example illustrates the need to consider the uncertainty to avoid "false negatives", that is chemical substances as non bioaccumulative while they have 75% of chance to be actually. Over the 211 chemical substances in the TK database, the Q75 criterion classifies a total of 28.9% of the chemical substances as "B" ($n = 61$).

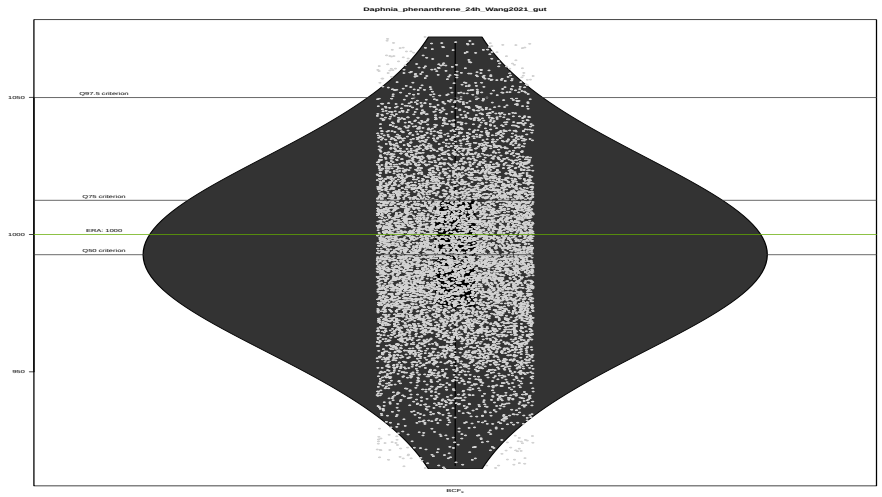

Fig. 3 Violin plot of the bioaccumulation metric posterior probability distribution for *Daphnia magna* exposed to phenanthrene (Wang et al., 2021). The green line symbolizes the threshold value at 1000 according to regulatory ERA, while grey lines stand for the 50^{th} (Q50 criterion in table 1), 75^{th} (Q75 criterion) and the 97.5^{th} (Q97.5 criterion) percentiles of the distribution, respectively.

Figure 4 shows another example with the genus *Enchytraeus* exposed to silver nano-particles (Topuz and van Gestel, 2015), illustrating the possible miss-classification of the bioaccumulative capacity of a chemical substance according to the Q97.5 criterion. Indeed, instead of being classified as "B" ($BCF \in [2000; 5000[$), silver nano-particles are considered as non bioaccumulative by both the Q50 (the ERA criterion) and the alternative Q75 criteria ($BCF < 1000$). In this case, the difference in the classification comes from a lack of precision of the BCF estimate which is associated with a large uncertainty range, that is the coefficient of variation (abbreviated as CV) is far over 0.5. This means that the BCF was delivered with a very dispersed probability distribution (Figure 4. The formula for CV writes as follows:

$$CV \simeq \frac{BCF_{\text{median}}}{97.5\%quantile - 2.5\%quantile}$$

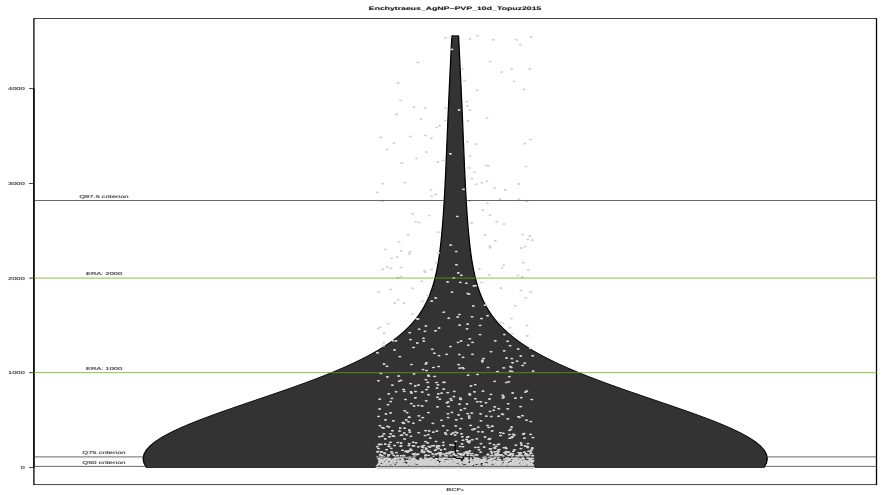

Fig. 4 Violin plot of the bioaccumulation metric posterior probability distribution for *Enchytraeus* exposed to silver nano-particles (Topuz and van Gestel, 2015). The green lines symbolize the threshold value at 1000 and 2000 according to regulatory ERA, while grey lines stand for the 50$^{\text{th}}$ (Q50 criterion), 75$^{\text{th}}$ (Q75 criterion) and the 97.5$^{\text{th}}$ (Q97.5 criterion) percentiles of the distribution, respectively (Table 1).

Considering all the 211 data sets available, we performed the classification of all chemical substances based on each of the Q50, Q75 and Q97.5 criteria, and compared the results in order to formulate sufficiently well-founded recommendations. As illustrated on Figure 5 concerning the genus *Anax* exposed to chlorpyriphos (Rubach et al., 2010), the classification was the same whatever the criteria. In particular, we assigned more than 90% ($n = 190$) of the chemical substances in the same class as done with the classical Q50 criterion (Table 1). These results support the use of the 75% quantile of the posterior probability distribution of the bioaccumulation metric estimates as a reasonable compromise between the classical median as currently required by the regulatory ERA, and the upper bound of the uncertainty range, while still accounting for the precision of the bioaccumulation metric estimates via the three-quarter quantile.

To summarize the whole database based on our recommended Q75 criterion, we finally classified 5.2% ($n = 11$), 9.5% ($n = 20$) and 14.2% ($n = 30$) of the chemical substances as "ℓB", "B" and "vB", respectively, confirming 71% of the chemical substances as non bioaccumulative. Regarding the precision of all bioaccumulation metrics, we got a high variability among species and chemical substances (see SI, see the .html file). Only considering the Q75 criterion, 37.4% ($n = 79$) of the chemical substances are associated with a $CV < 0.5$, with the most high CV among the "nB"-classified chemical substances (38.9%, $n = 82/150$). This reveals that when a chemical substances is considered as bioaccumulative, what ever the class, the corresponding bioaccumulation metric is precisely estimated in most of the cases.

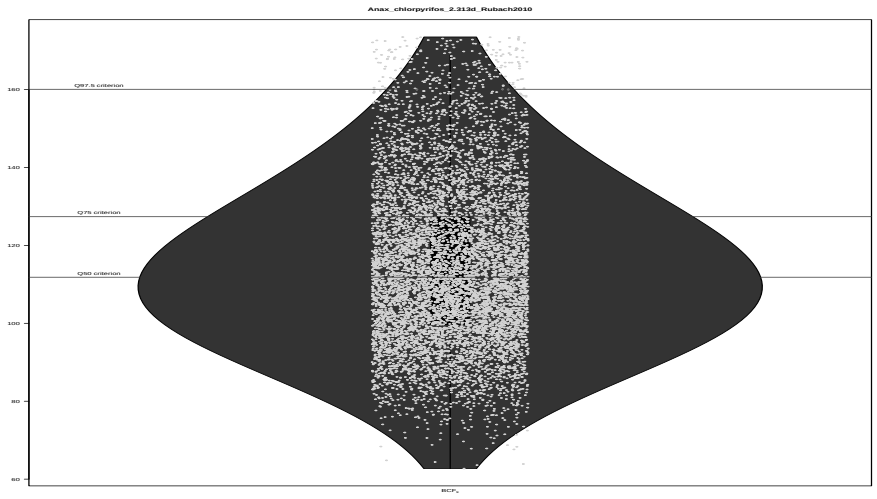

Fig. 5 Violin plot of the bioaccumulation metric posterior probability distribution for *Anax* exposed to chlorpyriphos (Rubach et al., 2010). The green lines symbolize the threshold value at 1000 and 2000 according to regulatory ERA, while grey lines stand for the 50^{th} (Q50 criterion), 75^{th} (Q75 criterion) and the 97.5^{th} (Q97.5 criterion) percentiles of the distribution, respectively (Table 1).

4 Conclusion

Based on a meta-analysis of a TK database comprising 211 data sets, this paper establishes how crucial it is to consider the uncertainty in classifying the chemical substances according to their bioaccumulative capacity. Thanks to the fitting of TK models under a Bayesian framework, delivering bioaccumulation metrics as probability distributions, this paper gathers together statistically-founded results towards the adoption a new criterion for this classification. Indeed, it can be recommended to use the 75% quantile of the bioaccumulation metric distributions in order to more precisely assign the chemical substances into the four regulatory ERA categories, that is as non-, low-, medium-, or very- bioaccumulative, and 90% in the same way as the current

approach required today. Also associated with precise estimates of bioaccumulation metrics, this new criterion would strongly improve ERA if it would be adopted by regulatory bodies. In addition, it could easily be implemented into the MOSAIC$_{bioacc}$ web service in support of the daily work of regulators when they need to quickly classify a set of several chemical substances.

Conflict of interest

The authors declare that they have no conflict of interest.

Consent for Publication

This manuscript has original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part.

Author Contributions

All authors contributed to the investigation of the TK database. Raw data collection and first analyses were performed by Aude Ratier and Sandrine Charles. The first draft of the manuscript was written by Aude Ratier and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Supplementary Information and data availability

Supplementary information is available at `https://doi.org/10.5281/zenodo.5865150`. All data used in this paper is downloadable from the MOSAIC$_{\text{bioacc}}$ web tool, directly from the associated TK database freely accessible at `http://lbbe-shiny.univ-lyon1.fr/mosaic-bioacc/data/database/TK_database.html`.

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