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Object: **revision on "Recommendations to address uncertainties..." submitted to PCI Ecology**

Dear Recommender,

Please find enclosed a revised version of our manuscript entitled "*Recommendations to address uncertainties in environmental risk assessment using toxicokinetics-toxicodynamics models*" and submitted to PCI Ecology.

A point-by-point list of changes is presented below according to the reviewers' comments.

Best regards,

Virgile Baudrot and Sandrine Charles

First of all, we would like to thank a lot the reviewers for their very positive comments and helpful suggestions on our manuscript. Every point has been addressed in the revised manuscript. Below, our answers are colored [in blue](#).

Recommender :

All three referees and myself consider the manuscript to be relevant and meritorious. Referee 1 had only minor comments to the manuscript and thought these minor comments did not justify a revision. Referee 2, in turn, had several comments, particularly with respect to more appropriately framing the contribution of the manuscript, and to improve Abstract, Discussion and Conclusion. Referee 2 also urged the manuscript to be reviewed by an expert in TKTD models. I then invited a third reviewer (Andreas Focks, who waived anonymity). He recognized the mathematical quality of the manuscript but made several suggestions to improve the clarity of the text.

Reviewer 1

This manuscript explores the use of TKTD models to reduce uncertainties in ERA. The topic is highly relevant and timely the more since the use of such models have (as the authors also indicate) been proposed for use by Legislative bodies such as EFSA in EU. The paper is very well written and besides a great overview of the state of the art, the case studies presented and discussed in the paper provide clear examples of the pros and cons of the methodology. My only (very minor) comment is that the paper is rather long, which is at least partly due that some text in the results section already discuss findings (e.g. P 12 Lns 260-264).

[We agree and following comments of other reviewers, we removed recommendations from results to gather it within the discussion part. We moved lines 260-264 to subsection 4.2, lines 284-291 to subsection 4.3 and lines 337-342 to 4.4.](#)

In addition, names of active substances should be written in small (not capital) letters (e.g. P 9 Lns 236/237).

[We agree and changed them accordingly.](#)

Authors also often focus on the use of the method for setting EQS (e.g. P 17 Ln 372), which implies that it would be especially useful for retrospective ERA. Although PNEC (which is not an EQS and especially used in prospective ERA) is mentioned, maybe indicating in the Introduction section that it can be used in both prospective and retrospective ERA would give more justice to this very interesting work.

[We agree that EQS may be differently defined depending on the context and institution \(EFSA, ECHA, WPS\). In the present manuscript, we use EQS as a global concept gathering all limit concentrations defined from exposure test without knowledge of the real-world exposure. We changed first lines of the Introduction.](#)

These comments, however, do in my opinion not justify recommending revision and I would therefore highly recommend this paper for colleagues working in this area and ERA in general.

We thank the reviewer for this very positive feedback.

Reviewer 2

I am not a modeler. I am a “seasoned” ecotoxicologist and will be reviewing the paper for issues pertaining to assumptions of the models, model predictions and ERA statements, and the general ability to communicate the story to the reader. Model equations and assertions in Sections 2 and 3 MUST be reviewed by someone qualified to do so.

General:

The authors address an extremely important issue of uncertainties in environmental risk assessments (ERAs) using toxico-models. They state they are recommending an “innovative approach” using a Bayesian framework – which is an excellent approach, but perhaps not innovative.

It is true, so in abstract, l.23, we changed "The innovative approach investigated in our paper is the use of the Bayesian..." into "We investigated the use of a Bayesian..."

They focus on lethality vs. time – which is an appropriate first stage approach. Nevertheless, the key issue in ERAs and the controversial issue in decision-making at contaminated sites is chronic toxicity – not acute toxicity.

l.37-38: in the introduction, we changed "Today, Environmental Risk Assessment (ERA) rests on fitting classical dose-response..." into "Today, one first step of Environmental Risk Assessment (ERA) is the hazard identification of acute effect which consists on fitting classical dose-response..."

The authors should acknowledge this and suggest further research in this area. The abstract leaves one “hanging” and should state explicitly what they are recommending and how they are moving science forward. The reader should not have to read the paper to find those answers!

We added the main recommendations in the abstract: "avoid computing $LC(x,t)$ and $MF(x,t)$ at extreme x values (0 or 100%) where uncertainty is maximal, compute $MF(x,t)$ after a long period of time to take depuration time into account and test survival under few correlated and uncorrelated pulses in term of depuration."

At the same time – the Conclusion (4.5) is completely void of specific conclusions from the paper. These must be stated explicitly – what did the authors develop in this Bayesian approach? How is it better? What are the uncertainties (do not simply refer to subsection 4.4.3)? and how will it improve ERAs? The meat of the paper is in subsections 4.3 and 4.4 (Discussion section), yet these need clarification and examples provided as they are confusing and not substantiated.

Our team already specifically studied the advantages of a Bayesian inference for ERA (Delignette-Muller et al., 2017; Baudrot et al., 2018c), and as previously discussed, many references have already done it.

We reformulated and developed the conclusion, where we also added:

"We showed that the degree of uncertainty can change dramatically with time and depending on the exposure profile, revealing that single values such as the mean or median may be totally irrelevant for decision making."

Specific:

1. The first paragraph of the Introduction is too long. Break it into separate thoughts.

We agree and broke the first paragraph into several smaller ones. Also, since we sent the manuscript to a professional reviewing service, some long formulations have been shortened.

2. Many of the acronyms being used, such as PNECs – are not being spelled out the first time they are used. In addition, they should be explained the first time used – as many will not understand what they are. In fact there is an excess of acronyms, making reading challenging. Get rid of some of these.

We totally agree, and it was also raised by reviewer 3. We replaced acronyms in the first sentence of the introduction, and for the whole manuscript, we kept only 5 of them: TKTD (Toxicokinetics-Toxicodynamics), GUTS (general Unified model of Survival), LC (Lethal Concentration), MF (Multiplication Factor), EQS (Environmental Quality Standard). Also, in the discussion, we removed all acronyms.

3. Lines 37- 38. The authors are incorrect in stating that ERAs rely on "fitting classical dose- response models to quantitative toxicity test data." This is but one SMALL portion of ERAs, and those conducting ERAs use a multitude of approaches, and consider chronic toxicity and ambient biological responses to populations and communities – when those data are available. The authors must tone- down their assertions. Their proposed models, if used, will be a small part of the ERA process.

We agree, and we rephrased these sentences to stress this point.

See L39-41:

From: "Today, Environmental Risk Assessment (ERA) rests on fitting classical dose-response models to quantitative toxicity test data. For acute effect assessment, [...]"

To: "Today, one first step of Environmental Risk Assessment (ERA) is the hazard identification of acute effect which consists on fitting classical dose-response models to quantitative toxicity test data."

4. While much of the paper is well written, there are occasional basic English mistakes which must be corrected. I will not list all of them.

As also suggested by the 3rd reviewer, we sent the manuscript to a professional reviewing service (see attached certificate).

5. Please read and incorporate the findings from the following paper, which is a summary of a U.S. EPA Science Advisory Board report dealing with the needs for improving ERAs: Dale VH, Biddinger GR, Newman MC, Oris JT, Suter GW, Thompson T, Armitage TM, Meyer JL, Allen- King RM, Benfield EF, Burton GA, Chapman PM, Conquest LL, Fernandez IJ, Landis WG, Master LL, Mitsch WJ, Mueller TC, Rabeni CF, Rodewald AD, Sanders JG, van Heerden IL. 2008. Enhancing the ecological risk assessment process. Integr Environ

Assess & Mgmt 4:306- 313. As you will find, the issues of temporal and spatial variance/characterization were recognized as a major uncertainty in ERAs and in need of improving. The authors study nicely addresses this need, but their recommendations should be placed in proper context with the many other issues associated with ERAs.

Thank you for mentioning this article that we added as reference in the revised manuscript. Indeed, it strengthens our approach by arguing the importance of studying uncertainty and probability in ERA since: "Assessments often fail to identify and prioritize uncertainties that could affect the quality of remedy decisions and additional information [...]". It also reveals the limitation of our study which would need to explore models including "spatial scale" and "multi-generational data". We mentioned both messages from this article in discussion (l.341-343 and 387).

6. In the introduction the authors spend some time noting how the Bayesian approach is superior. Many others have done this already in terms of ERAs and assessment of contaminated sediments.

We agree with this. We had in mind the work of Carlon et al. (2004) "Bayesian statistics-based procedure for sampling of contaminated sites", or Norrman (2004) "On Bayesian Decision Analysis for Evaluating Alternative Actions at Contaminated Sites" and for Bayesian interest in risk assessment, the highly cited paper by Siu and Kelly (1998) "Bayesian parameter estimation in probabilistic risk assessment" and for ERA specifically, the work of Wayne Landis and his collaborators.

We added the reference to Siu and Kelly (1998) which outlines motivations behind the Bayesian approach and provides guidelines to use it.

7. Line 366 - " may hide a very large uncertainty due to its limitation to 100% of covering." This makes no sense.

We agree and rephrased this part:

"[...], when the uncertainty is very large, predictions with their 95% credible interval are likely to cover all of the observations, even in case of low model accuracy. We showed that the WAIC and LOO-CV criteria are more robust probability measures for penalizing fits with large uncertainties [...]".

8. Lines 392- 394: Yes – but how are you addressing these uncertainties? You cannot – as they are often unknown.

We are not sure to properly understand this point. With TKTD models and our Bayesian approach, we have uncertainties around $LC(x,t)$ and $MF(x,t)$. So there are known.

Maybe the sentence was not clear, so we reformulated it:

l.373-376: "It appears that this uncertainty is maximal at the extreme (toward 0 and 100%) and limited around 50%. Since the point of minimal uncertainty may drastically change on the experimental design, it could be relevant to extrapolate the lethal concentration for a continuous range of x (e.g., 10 to 50%), as we did for Figures 1-(C,D)."

9. Lines 396- 400: This is hugely important and great that the authors note it – however

the last sentence does not make sense. If there is a multiplication factor to address these uncertainties – what is it and how can it be selected? It is doubtful that it has a scientific basis. I find this all quite concerning...

This last sentence was just here to introduce the next part (section 4.4). We addressed this question in this next section, so we changed and moved at the beginning of the next part.

10. Subsections 4.3 and 4.4: These subsections are VERY confusing and non-intelligible for the typical reader. It likely makes sense to the author, but not others. These should be moved to the end of the Results section and examples provided to support the statements being made.

Following reviewer 1, we moved some parts from results to discussion that we rephrased. As you can see in pdf with tracking changes, we totally reshaped all subsections 4.2, 4.3 and 4.4 of the discussion, to make it clearer.

11. The authors should feel free to share these comments with Theo Brock, as he understands the important issues and provided input on this paper.

We follow your suggestion and sent comments to T. Brock.

Reviewer 3 (Andreas Focks)

Recommendations to address uncertainties in environmental risk assessment using toxicokinetics-toxicodynamics models. The manuscript presents analyses of TKTD models for survival, i.e. the GUTS models, which investigate properties of these models in the light of regulatory risk assessment. Based on an earlier published and analysed example data set, the authors derive analytical mathematical solutions of the reduced GUTS models under constant external exposure and use these solutions in combination with the Bayesian inference method for model calibration and analyses of the propagation of parameter uncertainty to model predictions. Based on the derived mathematical framework, the authors analyse the uncertainty in model predictions for some scenarios, e.g. constant vs time-variable exposure, as well as properties of LC estimates over time, or as a function of the effect percentage. Further on, they test the effects of different time-variable exposure patterns on the model predictions. The manuscript shows a very good mathematical quality, and interesting analyses, which are relevant for the application of TKTD models of the GUTS type for the evaluation of toxicity tests.

The presented work is highly relevant and can be clearly recommended for publication in PCI ecology. Alone, the language is not fit for publication, and there are some formulations in the text which need to be rephrased in order to clarify the sentences or to avoid misunderstandings. In my review, I suggest some reformulations, and I corrected also some language issues, but I strongly recommend to let the manuscript be edited by a native speaker/expert.

We thank the reviewer for his positive comments. For the language issue, we sent the manuscript to a professional reviewing service (see attached certificate).

L7: As far as I'm aware of, EQS are used mainly in context of the European water framework directive, and much less in pesticide risk assessment. Therefore I would suggest to remove the term EQS from the text and to replace it by a more appropriate, e.g. just saying 'risk estimate'.

We think that "risk estimate" has a too large meaning since it would also cover the "exposure" modelling, what we do not consider in the present paper.

Also, as answered to reviewer 1, we agree that EQS may be differently defined depending on the context and institution (EFSA, ECHA, WPS) that we mentioned at the beginning of the Introduction. In the present manuscript, we use EQS as a global concept gathering all limit concentrations defined from exposure test without knowledge of the real-world exposure.

L.10 All suggestions on English grammar have been accounted for.

L10: the multiplication factors are for sure not a classical toxicity endpoint. Please re-formulate the sentence.

We agree and reformulated the sentence:

From: "The classical toxicity endpoints are the x % effect/lethal concentrations at a specific time t (EC/LC(x, t)), or the multiplication factors applied to environmental exposure profiles leading to x % of effect reduction at a specific time t (MF(x, t))"

To: "The toxicity endpoints include the classical x% effect/lethal concentrations at a specific time t (EC/LC(x,t)) and the new multiplication factors applied to environmental exposure profiles leading to x% effect reduction at a specific time t (MF(x,t), or denoted LP(x,t) by EFSA).

L12-14: What is likely to differ between species? Please formulate more clearly.

We meant observation time points which are likely to differ between species due to change in experiment duration (few days to several weeks).

Change: "[...] which are likely to differ between species (e.g. experiment duration)."

L.14 All suggestions on English grammar have been done. We only kept "EQS" rather than the proposition to use "risk estimates".

L32: All used acronyms are undefined here! Please either explain or leave out.

We agree so we defined and removed acronyms in this sentence. As suggested by reviewer 2, we removed some acronyms in the manuscript.

L.46: "the use of mechanistic models".

done

L52: this is very technical jargon, $x\%$ LC(x,t) etc. Is it possible to formulate this sentence (and also the abstract) in a more general, understandable way?

We agree and reformulated the text.

From: "[...] calculation of any $x\%$ lethal LC(x,t) or effective EC(x,t) whatever x and at any given exposure duration t."

To: "[...] calculation of lethal concentrations for any $x\%$ of the population at any given exposure duration t, denoted LC(x,t).

L59: "The GUTS-RED-SD model assumes..."

done

L71: "Quantifying uncertainties or levels of confidence..."

done

L96: "...data sets, as described in Ashauer et al. (2011) and Nyman et al., (2012).... testing in total five chemical compounds..."

done

Caption of Table 1: "and "Time points per profile" is the number of **observation** time points for each series (each constant profiles consisted **of** 5 time-points)."

done

L125/126: It could be useful to point to the fact that estimated DRT bare different for the SD and IT models, despite the TK model equations are identical.

We agree, and we added the sentence:

L.133-135: "While both GUTS-RED-SD and GUTS-RED-IT models have the same toxicokinetic equation (1), the DRTx likely differs between them since the meaning of damage depends on the toxicodynamic equations, which are different."

L163: '...where **the** Normalized RMSE...'

done

L167-169: Please give more precise definition of the PPC, including equations.

Our definition of the PPC is similar to the one provided in the Scientific Opinion (EFSA 2018) which is (page 48): "A basic technique for checking the fit of a model to observed data is to draw simulated values from the joint posterior predictive distribution of replicated data and compare these predicted samples to the observed data."

Also, while equations exist and are indirectly provided when we describe the prediction process

(section 2.3), it is a visual approach designed for assessors and stakeholders (see also Beck et al. (2016) arguing for the interest in visual approaches).

L171-175: Also for WAIC and LOO-CV it could be interesting to see the equation. In addition, could you state what is the range of typical or usual values for these two measures?

We agree, and we provided WAIC and LOO-CV computing in supplementary material.

However, there is no range of typical values of these two measures. Such as other criteria of goodness-of-fit like AIC or DIC, these values are used to compare models and not for the validation of a specific model.

L188: I tried to test equation 10, by filling in values to derive the LC, and ended up without results, because I needed to calculate t_z , which requires a water concentration C_w . I felt like this was circular equations, since the LC value should be the concentration leading to $x\%$ effect, but I need to fill in another water concentration?!?! I do not exclude that I was just not smart enough to apply the formula, but please point out better and in more detail how to use the equation.

It is true, derivation of equation 10 to obtain $LC(x,t)$ or $MF(x,t)$ is circular. Therefore, $LC(x,t)$ and $MF(x,t)$ formula are implicit equations. We assume the threshold concentration is reached in a finite time, so that when t tends to infinity, $t-t_z$ tends also to infinity.

Since, it was not said, we now clearly mentioned this assumption in the manuscript and in the Supplementary Material.

L189: "As mentioned in **the** Supplementary Material, under time-variable exposure, t_z is also variable with time, while in the case of constant exposure, t_z is exactly $-1/kd \ln(1 - z/C_w)$. For increasing time, the LCSD (x, t) curve becomes a vertical line at point z , and **for infinite time**, the convergence is:"

done

L201-202: What do you mean by the last sentence, I do not understand. Please reformulate or delete.

It's true, this sentence was not relevant here, introducing confusion, so we removed it.

Eq 17: Same issue with calculation of t_z as described above.

As for equation 10 and its use, equation 16 and its derivation (equation 17) are implicit equations due to t_z . Also, since the equation 17 was not used in the manuscript, we moved it in the Supplementary Material.

L224 ff: "For all compounds, fitting **on observed survival from testing under** constant exposure profiles provides better fits than for **using data from testing** time-variable exposure profiles "

done

L232-234: I do not understand the meaning of this sentence, please formulate more clear or delete.

We agree, this sentence was not clear, and we reformulated it.

L238-242: All suggestions have been taken into account.

We also reformulated the paragraph, l.251-253: "However, when uncertainties are large, the 95% credible interval around predictions used for the PPC tends to cover all the observations regardless of the fitting accuracy. The Bayesian measures WAIC and LOO-CV are better for penalizing excessively large uncertainty."

L248: Rarely analysed?

yes, we replaced the expression.

L250/251: Here and in many other places in the discussion, it is unclear whether you speak about uncertainty or variability. When I assume that uncertainty is the credible area around the median prediction, this sentence is not true. When you want to say that in the beginning of the tests the LCX values change quickly for increasing experimentation time, this is correct, but needs to be formulated more precisely!

We totally agree with this, there is a mistake here.

In the text, we talk about "uncertainty" when it refers to the credible interval around the median (grey band). We talk about "sensitivity to a parameter p", when focusing on the response to a little change in "p". In the present manuscript, it is always a "sensitivity to time".

So, L262-265, we changed the following sentence:

From: "A direct consequence for risk assessors is that evaluation of $LC(x, t)$ at early time induces higher uncertainty than at a later time (specific time being relative to the species and the compound). In other words, the sensitivity of $LC(x, t)$ to time t decreases as long as t increases."
To: "A direct consequence for risk assessors is that evaluation of $LC(x, t)$ at an early time induces higher **sensitivity to time t** than that at a later time (with the specific time being relative to the species and the compound). In other words, the sensitivity of $LC(x, t)$ to time t decreases as long as t increases."

We also reviewed all the manuscript to remove such mistakes and to clearly write "sensitivity **to time**". See lines 389, 409 and 413 where we talk about sensitivity to time for outputs $LC(x, t)$ and $MF(x, t)$.

L254-256 Here you argue against L250/251. Please streamline this section and check the use of the words uncertainty and variability!

Now, with the previous correction, this sentence is correct without contradiction. It is about uncertainty, l.267-269: "However, note that the uncertainty of LC(x, t) does not always decreases when time increases. For instance, as shown in Figure 1-(B), the uncertainty at day 6 and afterward is greater than around day 3."

L262-264: "At least, we recommend to look at the LC(x, t) at the last time of the experiment, what is in line with the common procedure in ERA." It sound a bit funny that you recommend something that is already done. A possible rephrasing could be "Our analysis confirm that the evaluation of experimental data at the last day of an experiment is supported by theoretical considerations."

We agree, and we reformulated this sentence now in discussion, section 4.2 lines 390-393.

L272-274: It is not clear what the recommendation is here. Calculate LCX values for different X values for each experiment? This is not useful. Please comment on that in the text.

Yes, it is true. This sentence, repeating previous statement about optimality of x% value for LC(x,t), introduced confusion, so we removed it.

L278-279: I do not agree that the later the lower. There is a shift down in 2E and 2F, but then the MF is constant again. Please be more precise in the formulation.

True. We rephrased for part and removed the last sentence:

From: "As expected, Figures 2-(D-F) show that the multiplication factor is decreasing when the time at which the survival rate is checked increases. In other words, the later the survival rate is assessed, the lower is the multiplication factor."

To: "As expected, Figures 2-(D-F) show that the multiplication factor **decreases, or stay constant**, when the time at which the survival rate is checked increases."

L282: Replace 'surrounding' by 'at the time of exposure'

done

L283 ff: All suggestions have been done.

L285-287: Please check the language/formulations in this sentence.

We moved this part in discussion and rephrased as follows:

From: "More generally, the multiplication factor is designed to be compared with the assessment factor (AF) classically used in concert with the effect/lethal concentration value based on realistic time-variable exposure profiles to derive an EQS."

To l. 416-19: "More generally, the multiplication factor is designed to be compared to the assessment factor (AF) classically used with the effect/lethal concentration value to derive EQSs based on real-world exposure profiles."

L290: "describe"

done

Figure 3: replace 'half-life' by dominant rate constant. Correct inlay: GUTS-SD is GUTS-RED-SD and the same for IT. The same also for figure 4.

Yes, we changed in Figure 3. And we replaced GUTS-SD by GUTS-RED-SD, GUTS-IT by GUTS-RED-SIT in every Figure.

Figure 5: caption: "respectively"

done

L318: "for the Malathion..."

done

L318-321. I do not understand what you mean here. Please formulate more clear!

We rephrased it as, l.318-320: "Since there is the cumulative amount of contaminant is not changed, we do not see any effect of contaminant depuration (equation 3 and Figure 3), which could help individuals recover under a lower frequency of peaks."

L336: "Again, because of the different depuration times of the two GUTS models..."

done

L346: "noise"

done

L347: "tracking how uncertainty propagates"

done

L358: "Our study confirms that under specific consideration of uncertainties in regulatory toxicity endpoints no evidence to choose one of the GUTS-SD or GUTS-IT models over the other is given."

done

L360/361: Please clarify that the more conservative model should only be used if successfully validated.

We changed into, l.354-356: "A simple recommendation is therefore to use both and then, if they are successfully validated, take the most conservative scenario in terms of the ERA."

L365: I'm not sure whether the PPC can be easier interpreted as e.g. the NRMSE, since also this indicator can be shown visually.

The reference we used (Beck et al., 2016) argues for the use of visual plot. PPC is a classical Bayesian for a visual comparison of prediction with observations in and out of the predicted area. However, we clarified that it was compared to WAIC and LOO-CV which are much more complicated to use:

"[...] and is therefore easier to interpret, compared to Bayesian WAIC and LOO-CV, for risk assessors and stakeholders (Beck et al., 2016)."

L369: Please add that the NRMSE was just recommended to be used in the recent EFSA scientific opinion on TKTD models.

done

L384: replace 'decay' by 'decrease'

done

L384 ff: Please check here also the use of the term 'uncertainty'; I think you speak about variability of the value, not about the uncertainty as expressed in credible intervals.

It is true. As previously detailed, we talk here about 'sensitivity to time t'. Thank you for having pointed this.

L394: Please write a correct end of the sentence.

done

L400: Please add the recent EFSA scientific opinion on TKTD models to the citation of Ashauer 2013. Ashauer used the term margin of safety, and the SO defined the multiplication factors.

done

L402-411: Please check whether you replace $MF(x,t)$ and $LC(x,t)$ by verbal descriptions, otherwise the section is hard to read. E.g. time-and level specific multiplication factor or lethal concentration.

We agree, and we chose in the discussion to remove mathematical notations.

L408: 't goes to a long time'. Please replace by 'for long times' or similar.

We replaced by "when time goes to infinity".

L412-417: I do not understand this section. Isn't it clear that the MF is changing abruptly in response to a peak? Still, the MF at the end of a tested exposure profile is most relevant, and since the computation of the MF all over time as you suggest is computational intensive, I do not see the advantage of this, but only confusion and increased effort. Please consider to change this section accordingly.

We agree and removed the last sentence of this part. Since reviewer 2 also mentioned this section was not clear, we drastically changed this part.

L424: 'scaled internal concentration' is not the updated terminology (Jager and Ashauer 2018), please check!

True, it is now "scaled damage". We changed it.

L424-431: Please check language and formulate more clearly what you want to say., I do not understand the meaning of this section.

We agree this part was confusing, so we changed it.

L444: 'uncertainty of predictions under time-...'”

done

L457: 'thousands'

done

L479: 'do not always follow'

done

L491: Since the content of the manuscript uses a lot from the recently published EFSA SO on TKTD models (e.g. multiplication factors, NRMSE), it would be only fair to acknowledge this by citing it in the conclusion paragraph.

We totally agree and mentioned that our study was inspired by the recent EFSA report in conclusion, and also in the introduction. This is made now easier as the EFSA SO is available.