NTTPs – vegetative vs. reproductive endpoints - Is the potential increase in protectivity an indication of sensitivity or of relevance? (modelled vs. real data)

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INTRODUCTION

Herbicides are currently assessed for effects on non-target terrestrial plants (NTTP) by testing vegetative endpoints (e.g. shoot height, biomass). If reproductive endpoints (e.g. no. of flowers, seed biomass) were tested in addition, and the lower be used in the risk assessment, the level of conservatism would increase. If reproductive endpoints are more sensitive then their inclusion would impact the risk assessment. To assess the likely impact of generating additional data in this paper we generated artificial data (“Var 1”) and modelled inclusion of an additional second endpoint “Var 2”) with exactly the same sensitivity and scatter as the first, and assessed the effect of this additional data has on the overall regulatory threshold.

Fig. 1. Vegetative endpoint (court. IBACON)

Fig. 2. Reproductive endpoint (Skitterphoto)

MATERIAL & METHODS

For the modelling approach we generated random log-normally distributed data (Var 1 & Var 2) with the same mean and spread, but considering the two variables are not independent: a potent herbicide with a low vegetative endpoint will also have a relatively low reproductive endpoint, whereas a less potent herbicide with a high field rate also tends to have higher endpoints. The spread between the two thus also followed an – albeit narrower – log-normal distribution; the spread could be varied. With the resulting modelled data (Figs. 1 A - 1 C) we repeated the what-if analysis previously performed on real data (vegetative vs. repro.-NTTP data (EFSA 2014[1], Christl 2018[2]) and compared the outcome based on modelled and real data, both from the EFSA-database and from our data base in parallel.

RESULTS

Modelled data (random distributions), A: as generated; B: sorted by ratio Q; C: sorted by potency.

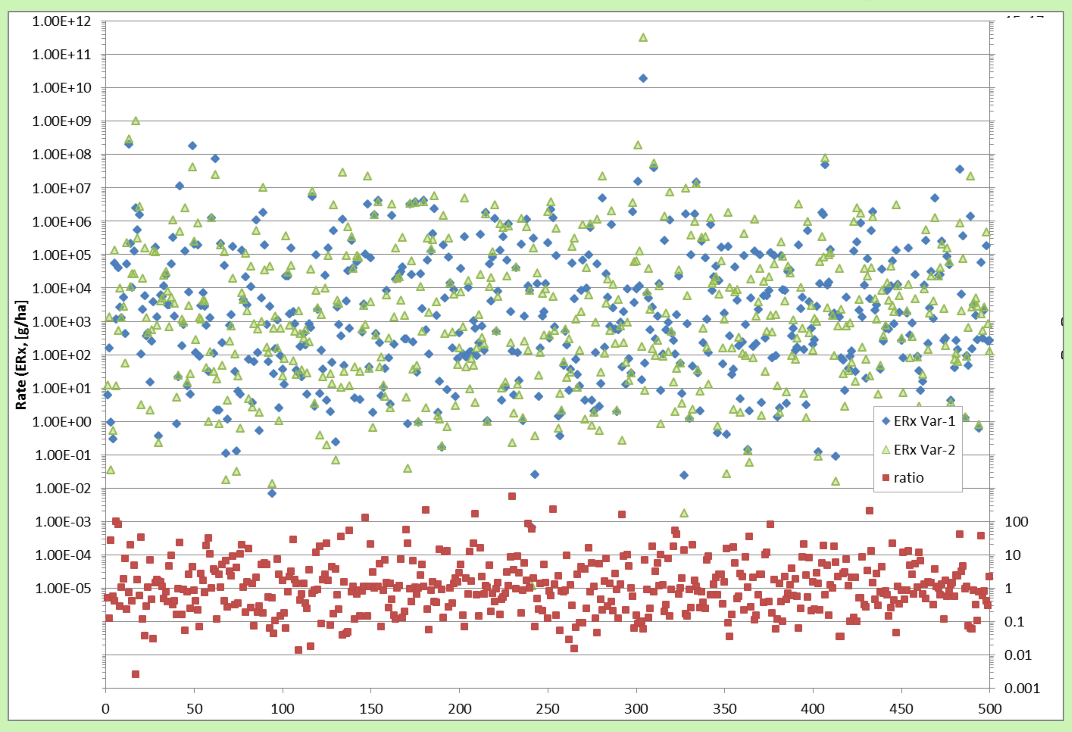


Fig. 1 A). Artificial data (Var1, Var2 and ratio (Q) between the two), unsorted.

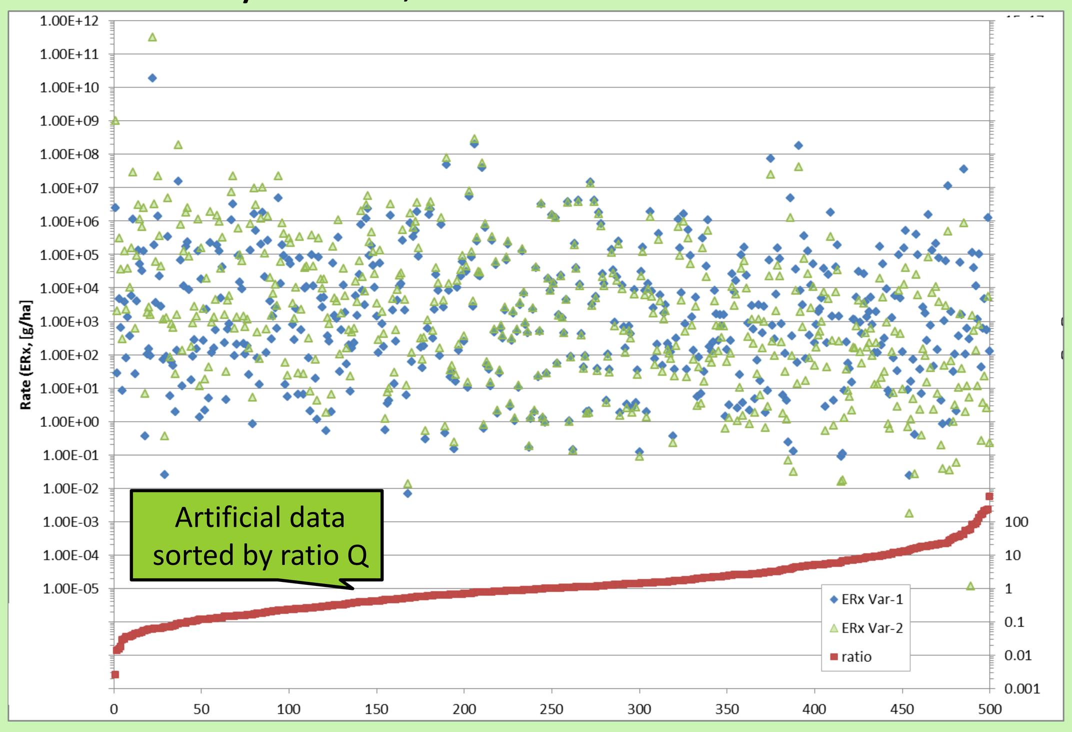


Fig. 1 B). Artificial data (Var1, Var2 and ratio (Q) between the two), sorted by Q.

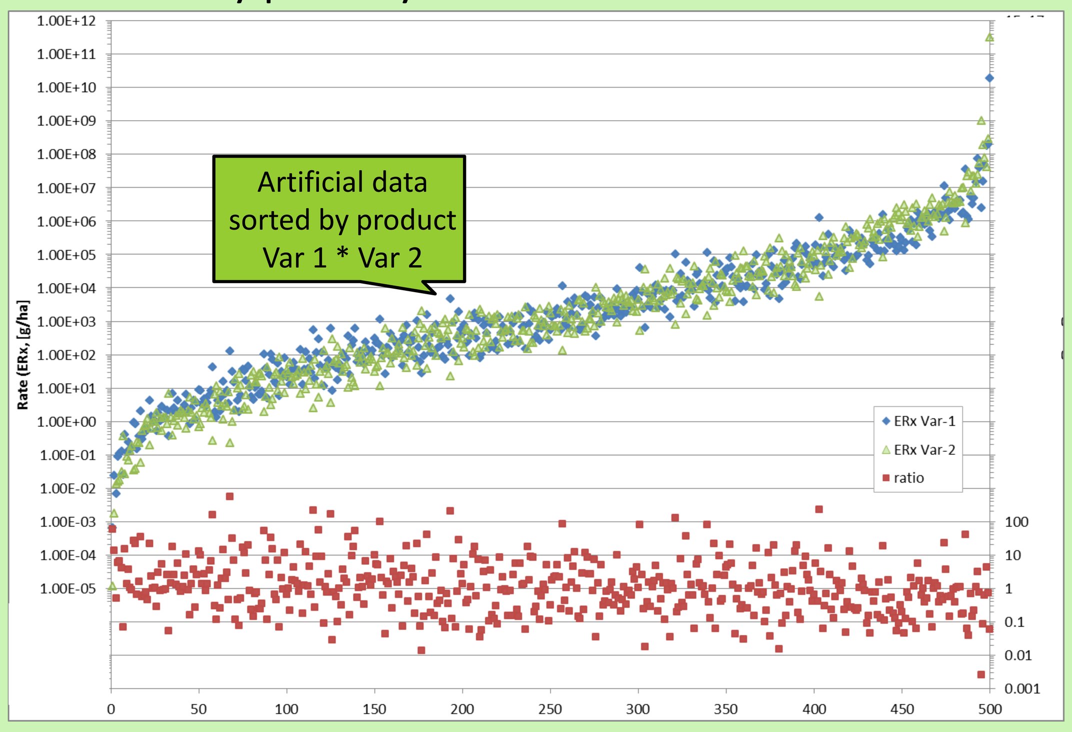
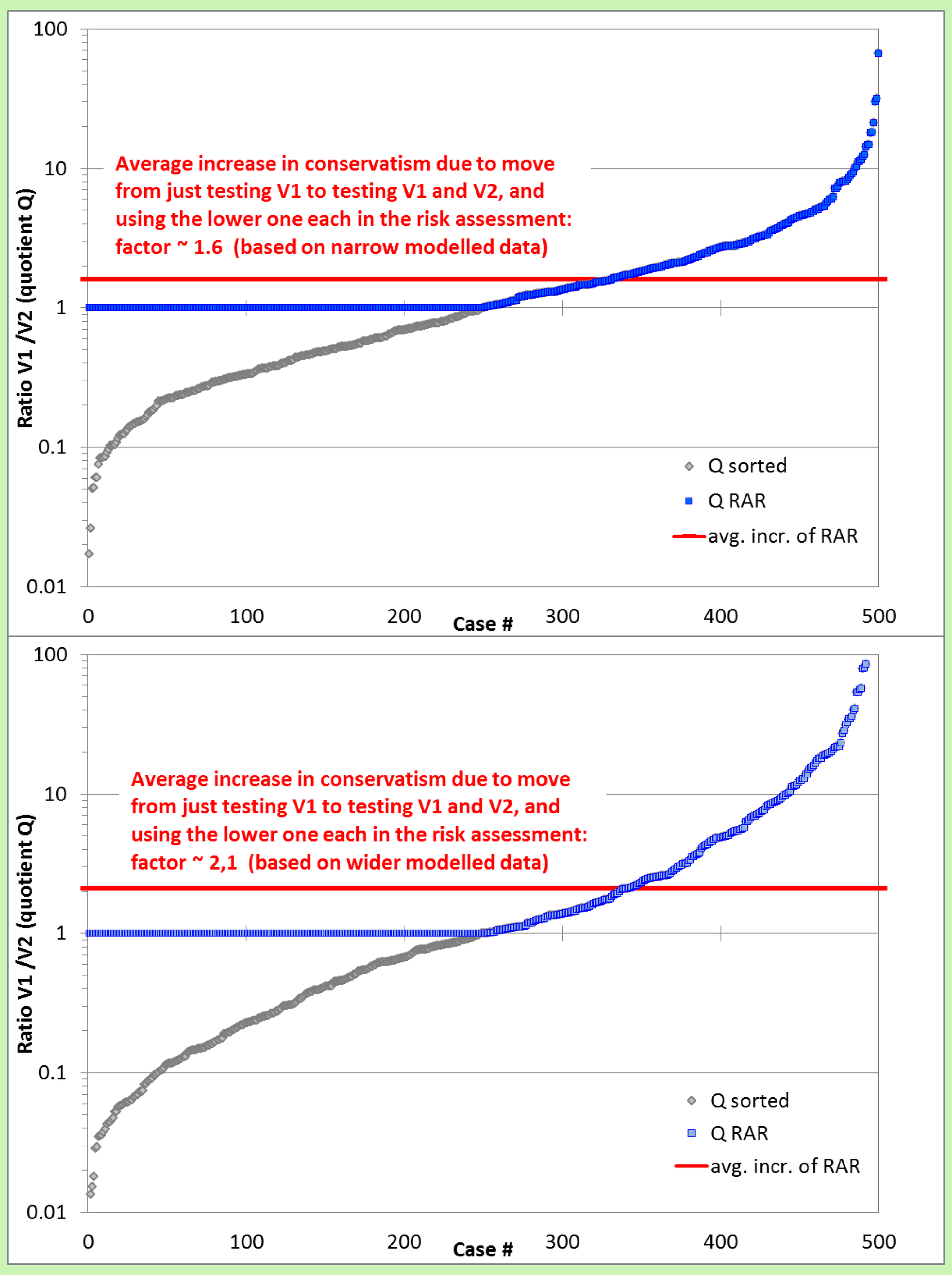


Fig. 1 C). Artificial data (Var1, Var2 and ratio Q), sorted by Var 1 and 2

RESULTS

What-if analysis – modelled data: Var1 vs. Var2



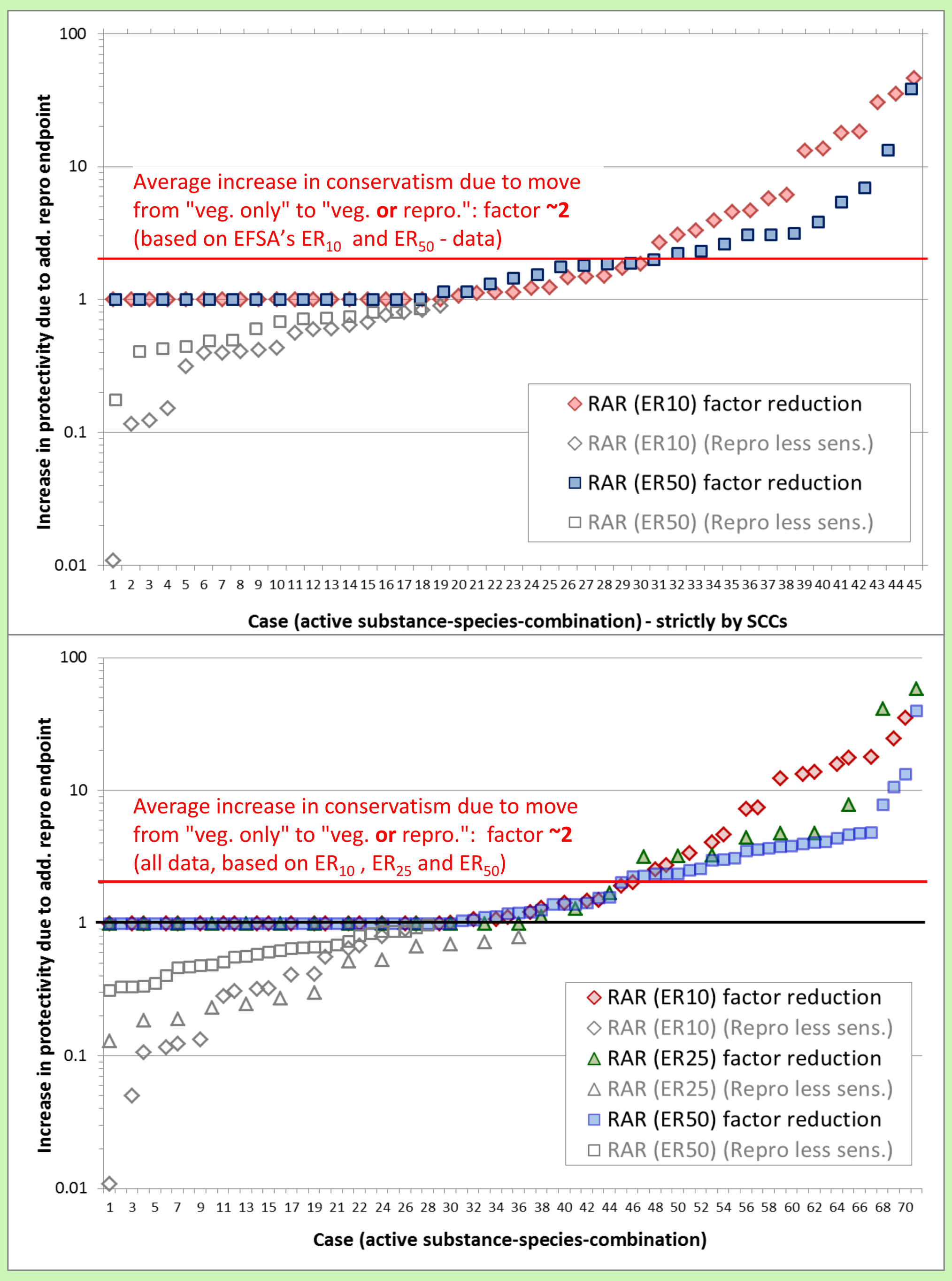
Figs 2 A + B **Artificial data, Q ascending, & increase of conservatism:**
Opt. A with less scatter (narrow distribution of Q, flat curve); Var 1 and Var 2 close to each other.
Opt. B with higher scatter (wider distribution of Q, steeper curve); Var 1 and Var 2 less similar.

RESULTS

What-if analysis – real data: vegetative vs. repro

A) → EFSA data only

B) → All data, including EFSA’s



Figs. 3 A + B: **Quotients Veget./Repro. in ascending order, depicting the factor by which the conservatism at tier1 would increase if the reproductive end-point were always tested and in cases where the reproductive endpoint is more sensitive (quotient Q is greater than 1). Where the reproductive endpoint is less sensitive, the conservatism factor is set to 1 (no change of the RAR). The grey signatures indicate by which degree the reproductive endpoint was less sensitive than the vegetative endpoint.**

RESULTS

Quotients of artificial data (Figs. 1 A – C) if plotted in ascending order (Fig 1 b) do form sigmoidal curves (Figs. 2 A + B) very similar to the corresponding plots of the real data (Figs. 3 A + B). Quotients below 1 (new Var2-endpoint e.g. reproductive) not lower than existing (Var1-endpoint e.g. vegetative) lead to no change in the risk assessment (no increase in conservatism, Q = 1) whereas if the new endpoint Var2 is more sensitive, the conservatism would increase by Q. The overall increase of the protection level solely depends on the average spread between Var1 and Var2. The more similar the two are, the lower the overall change (Flat curves vs. steeper curves, Figs. 2 A + B, and in Figs. 3 A+B compare slopes of ER50 , ER25 and ER10).

DISCUSSION

The patterns observed (Figures 2 A + B) are strikingly similar to the real data collected by EFSA[1], Fig. 3 A) and by us[2] (Fig. 3 B). The increase in conservatism predicted would also be achieved if two endpoints (instead of just one) with the exactly identical sensitivity and scatter were generated. Our analysis shows that for the actual data collected by EFSA and also our data there is no indication that the reproductive endpoints are more sensitive than the currently assessed vegetative ones, nor do they indicate that the reproductive endpoints add a fundamentally new quality to the risk assessment. The analysis of the artificial data demonstrated that just testing the same variable twice (or testing two variables with the same sensitivity & scatter) would lead to an increase in conservatism by a similar magnitude as the one observed in the real data sets. Modelled and real data also illustrate that ER10 endpoints bear considerably more uncertainty, so are less reliable than ER25 or ER50 data.

CONCLUSION

Based on two plant databases, differences between ER_{50}, ER_{25} and ER_{10} values were detected, but hardly any between reproductive and vegetative endpoints. EFSA’s proposed use of reproductive endpoints would still increase the margin of safety (on average by a factor of 2) if two endpoints are tested, and the lowest of the two is used in the risk assessment. This predicted increase in protectivity does however not indicate that reproductive endpoints are more sensitive or add a new quality. Artificial data demonstrate that just testing the same variable twice or testing two variables with the same sensitivity and scatter would also lead to an increase in conservatism by a similar magnitude. We therefore question that including reproductive endpoints as a standard requirement in the risk assessment procedure would be worth the effort. Reproductive endpoints bear more intrinsic variability and cause a multitude of problems (invalid data, lack of guidelines for reproductive tests, costs...). A move from ER_{50} to ER_{10} would increase conservatism but also increase uncertainty. The combined changes proposed by EFSA would increase the conservatism of the Tier 1-RA by a factor of 5 to 8, and the *addition* of reproductive endpoints alone only by a factor of 2. A move to ER_{25} could utilize data generated for the US, increase conservatism & avoid uncertainty inherent to ER_{10}. Also keeping the “vegetative ER_{50}” but increasing the assessment factor would be more expedient than a change to “reproductive ER_{10}”.

References:

[1] EFSA 2014. Scientific Opinion addressing the state of the science on risk assessment of plant protection products for non-target terrestrial plants. EFSA Journal 2014;12(7):3800, 163 pp. doi:10.2903/j.efsa.2014.3800 .

[2] Christl et al. 2018. Comparative assessment of vegetative and reproductive terrestrial plant species endpoints of plant protection products – a literature review. IEAM, in preparation. (Christl 2017 Workshop Report)

Acknowledgements:

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