

Analysis procedures and corresponding software tools are presented to improve current practice of dose-response analysis to fit to the new recommendations of EFSA 2019.

Towards a More Reliable and Appropriate EC_x Endpoint Derivation Scheme

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INTRO

EFSA 2019: “Pesticides Peer Review Meeting on general recurring issues in ecotoxicology” discussed the reliability of EC_x calculations.

From this open question are:

- A smaller normalized width is always more reliable?
- The lower limit of EC_{10} CI is always more suitable for risk assessment when the CI of EC_{20} includes EC_{10} ?
- Which model to choose? Which confidence interval to present?

METHODS

1. Simulation examples and real data examples indications and impacts of the reliability criteria
2. Confidence intervals can be also derived using robust methods.
3. Back calculation of the regulatory EC_x defined relative to the control.

- Inhibition effect

$$EC_{trueX} = EC_{software} \left\{ x \cdot \frac{d}{d-c} \right\}$$

- Increasing Effect:

$$LD_{trueX} = EC_{software} \left\{ x \cdot \frac{1-c}{d-c} \right\}$$

RESULTS

- An R package is developed to assist the calculation of EC_x , within regulatory context. (available currently upon request)
- Multiple possible model could and should be fitted at the same time.
- Selection of the model should be based on multiple criteria shown in Table 1.
- Regulatory EC_x is automatically back-calculated from the fitted models.

Model	IC	Lack of fit	Certainty Protection	Steepness	No Effect
W2.3	284.351	0.086	Medium	Shallow	0
EXD.2	285.272	0.058	High	Shallow	0
LN.3	285.287	0.062	Medium	Shallow	0
LL2.3	285.581	0.056	High	Shallow	0
LL.3	285.581	0.056	Medium	Shallow	0
W1.3	286.024	0.047	Medium	Shallow	0

Table 1: Multiple Fitted Models with the Criteria defined in EFSA 2019 and AIC, Lack-of-fit test p-value, trend test p-value. Does response in Fig 2.

DISCUSSION

- A smaller normalized width \neq Better Model
- Case-by-case discussion is necessary especially when choosing 4-par models and when the overlapping of CIs

Illustration of Difference between Regulatory and Software EC_x

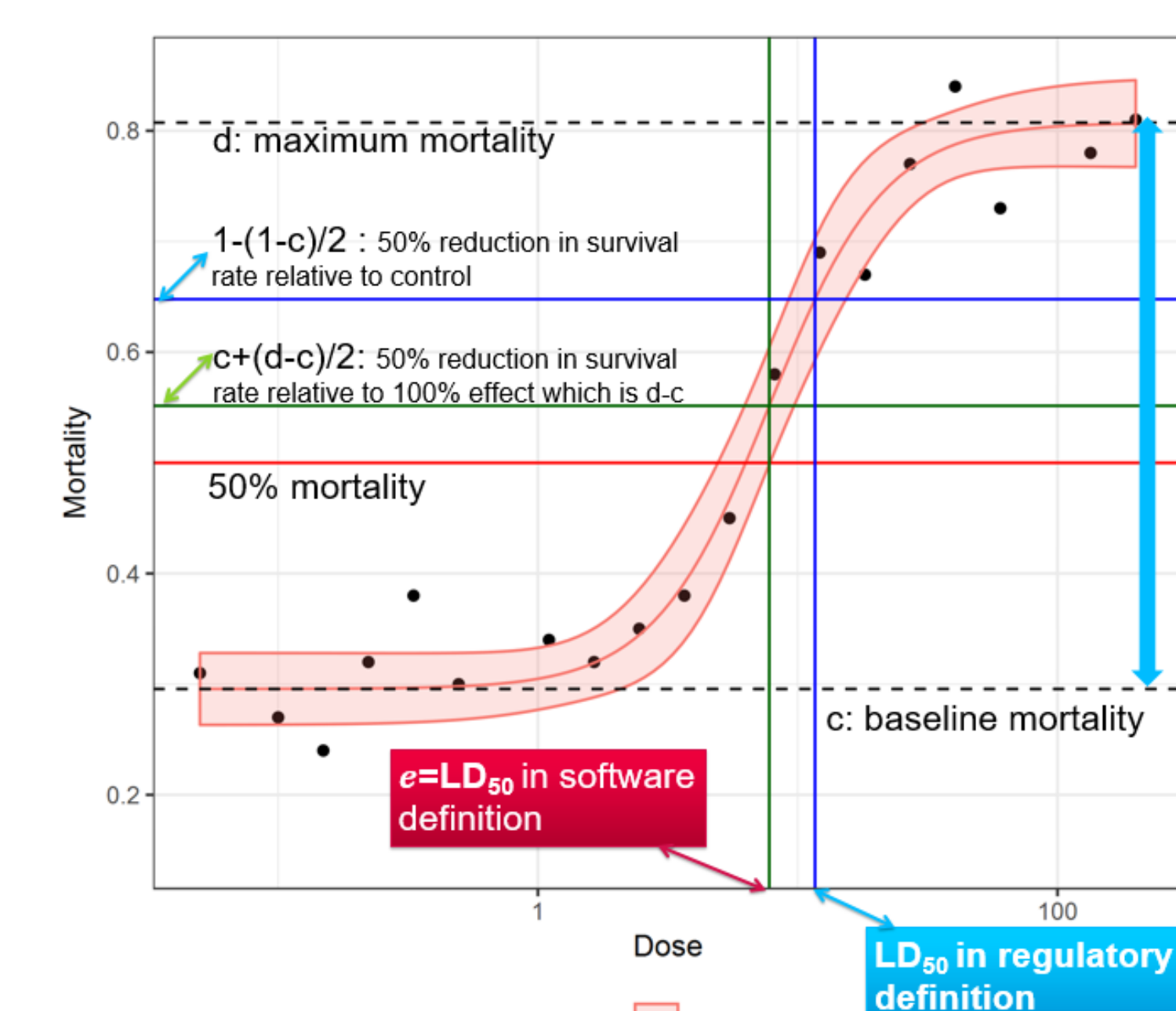


Fig 1: Schematic plot of simulated data from a 4-par log-logistic model with binomial error assumption.

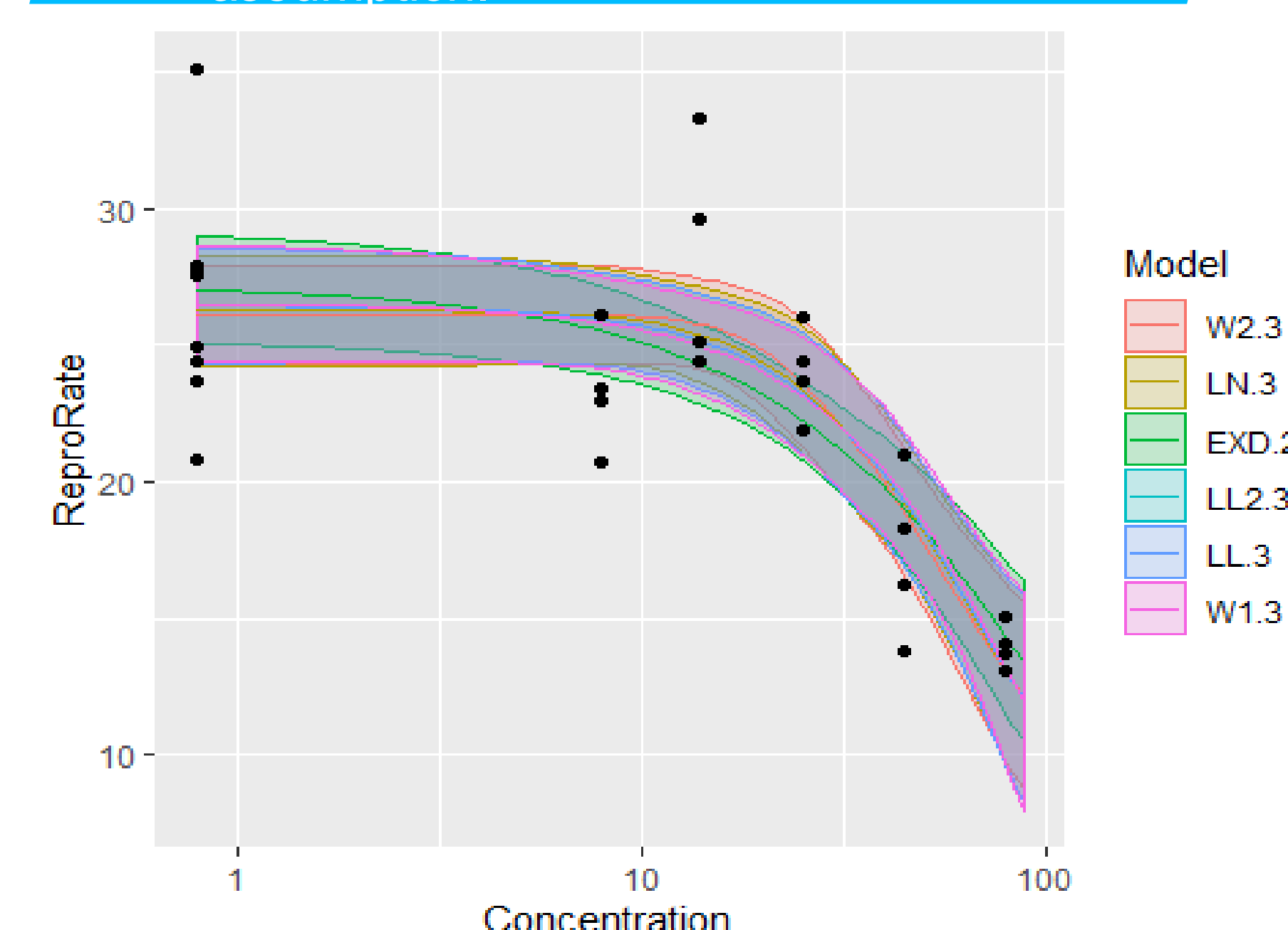


Fig2 : Multiple Fitted Model Plotted Together.

Model	Estimate	Lower	Upper	NW	Rating	EC
W2.3	26.02	14.65	37.39	0.874	Fair	EC 10
	36.49	24.54	48.44	0.655	Fair	EC 20
	80.81	51.44	110.2	0.727	Fair	EC 50
EXD.2	13.29	8.367	18.21	0.741	Fair	EC 10
	28.15	17.72	38.58	0.741	Fair	EC 20
	87.44	55.05	119.8	0.741	Fair	EC 50
LN.3	24.21	9.45	38.97	1.219	Poor	EC 10
	36.6	21.46	51.75	0.828	Fair	EC 20
	80.72	54.2	107.2	0.657	Fair	EC 50

Table 2: EC_x Estimation with confidence intervals derived from multiple fitted models.

