

RP101 Well Past Time To Stop Using NOELs and LOELs ([download paper at-http://onlinelibrary.wiley.com/doi/10.1002/ieam.249/abstract](http://onlinelibrary.wiley.com/doi/10.1002/ieam.249/abstract)).

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Introduction-

We should not even be having this discussion

Researchers have warned of the dangers of using hypothesis testing to describe an exposure-response curve. The citations cover much of the last 60 years. These citations include: Skalski 1981; Stephan and Rodgers 1985; Leisenring and Ryan 1992; Hoekstra and Van Ewijk 1993; Laskowski 1995; Chapman et al. 1996; Kooijman 1996; Suter 1996; Moore and Caux 1997; Crane and Newman 2000; Pires et al. 2002). Two recent textbooks point out the lack of technical defensibility of NOELs and LOELs (Newman 2010; Landis et al. 2011). Despite this accumulating evidence, NOELs and LOELs continue to be widely used in the field of ecotoxicology. In May 2011 these were the total citations for NOEC in the two SETAC journals.

| Search Term NOEC, 23 May 2011 | |
|---|---------------|
| <i>Environmental Toxicology and Chemistry</i> | 588 citations |
| <i>Integrated Environmental Assessment and Management</i> | 73 citations |

Exposure-Response

It's the curve!

The problem with NOELs and LOELs is basic. The fundamental model of environmental toxicology is the exposure-response (or concentration-response or dose-response) curve that describes the relationship between exposure and effect. It is a given that the best possible description of this relationship must be the keystone of the field of toxicology. NOEL and LOELs do not meet the criterion of adequately describing the exposure-response curve.

Exposure-response curve is one of the basic tenets of toxicology-the dose makes the poison (Paracelsus 16th century).

Example curve from Moore and Caux 1997-see references

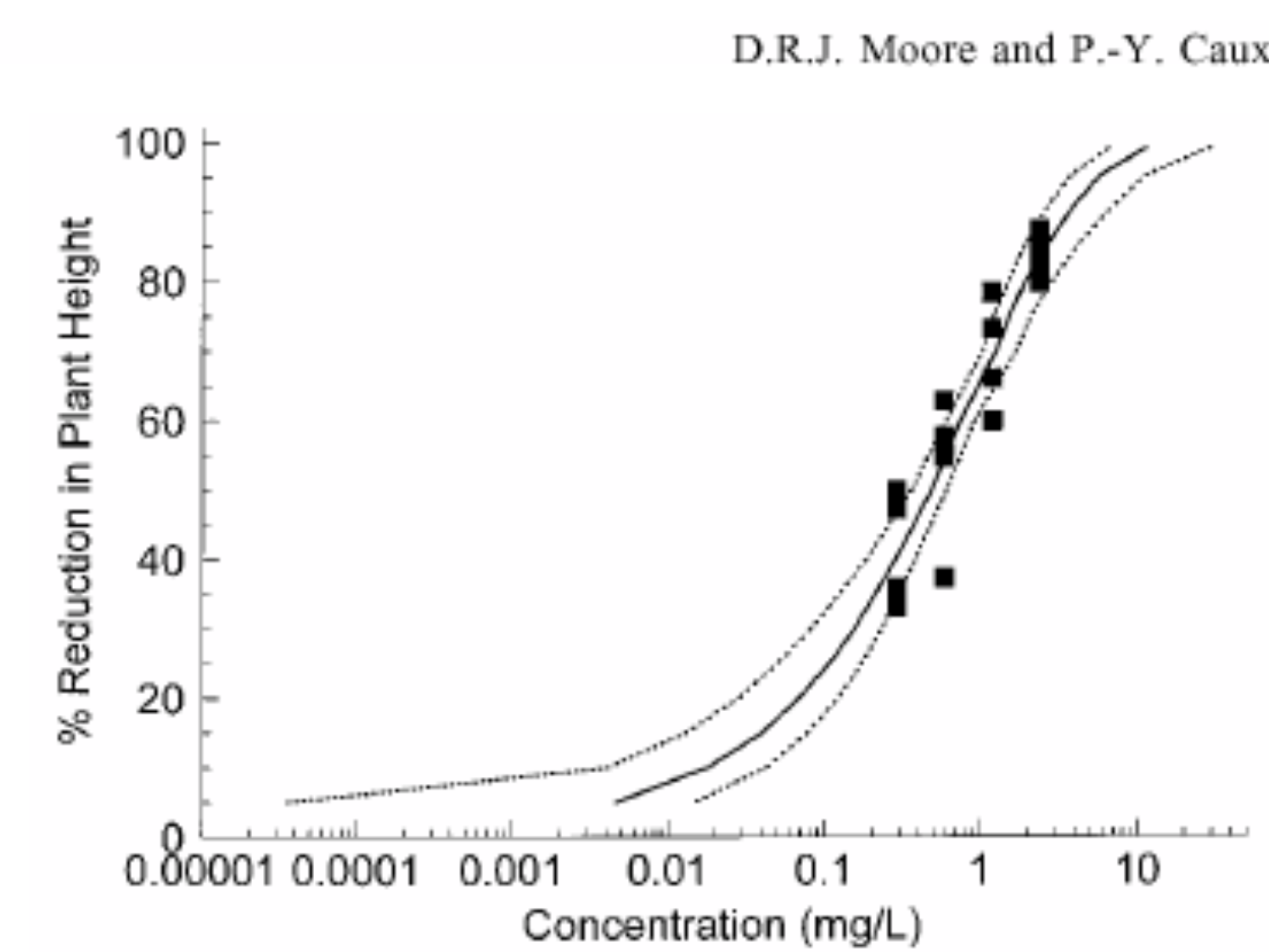
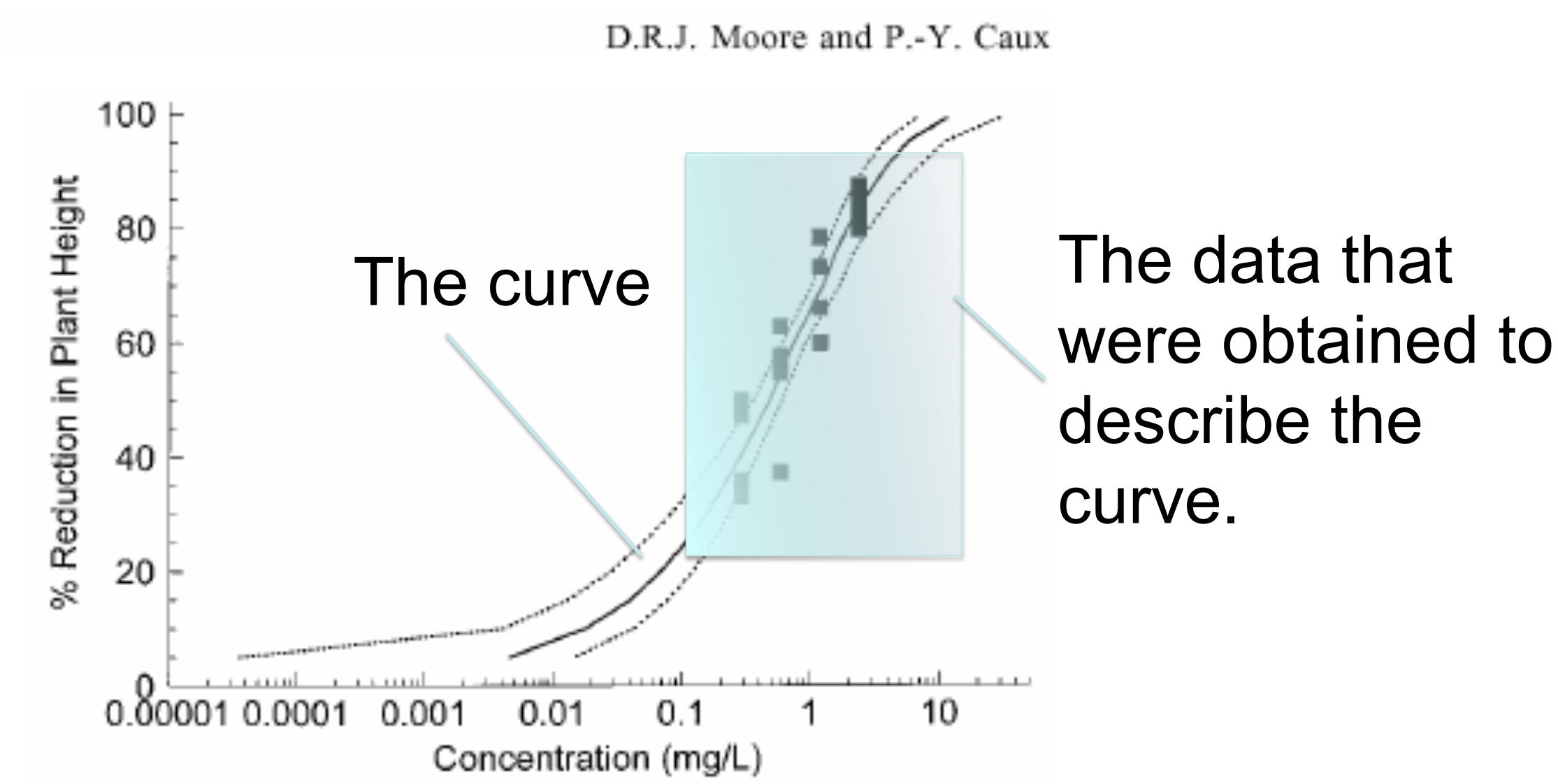
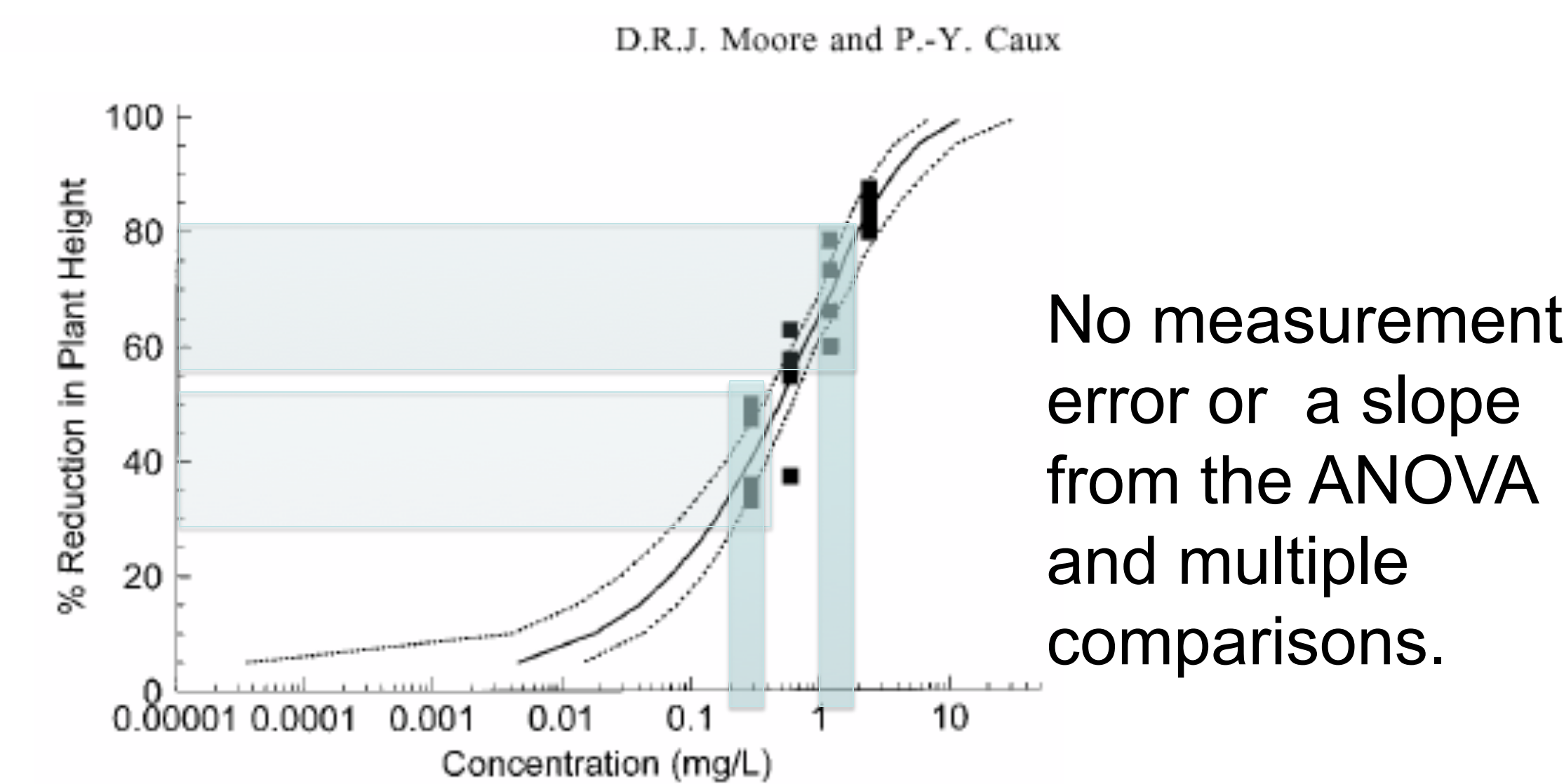


Fig. 7. Concentration-response curve with 95% confidence limits for reduction in soybean plant height as a result of a 21-d exposure to pesticide D-54 following germination.

Data are taken to estimate the parameters of the model - the curve.



Derivation of the NOEL/LOEL-hypothesis about projections of the data based on treatment groups.



There is not a hypothesis regarding the exposure-response curve

NOEL/LOELs are not descriptions of curves and are not data.

- 1) NOELs and LOELs are not measurements with an associated standard error or deviation.
- 2) They are not data and are not connected with measurement error.
- 3) They are not direct observations, but are simply labels for experimental treatments.
- 4) Yet, these labels of treatment groups are often used as if they were data in species sensitivity distributions and other data compilations.
- 5) These compilations appear scientific but sacrifice the exposure-response underpinning of toxicology.

Derivation of exposure-effect curves is not new.

Litchfield and Wilcoxon (1949) graphical derivation of exposure-response with confidence intervals is a citation classic with over 5,000 listings.

Stephan (1977) reported methods for calculating median lethal concentrations (LC50s) that involved both curve-fitting and the calculation of confidence limits.

Twenty six years ago Stephan and Rodgers (1985) showed the power of the regression approach in the analysis of chronic toxicity data.

Moore and Caux (1997) demonstrated the ability to model exposure curves for a wide variety of data sets.

Curves are generated by undergraduate researchers.

D. magna reproductive toxicity test Mariana Cains SETAC Boston 2011 see Poster RP269)

GraphPad, SPSS and many other packages can perform the calculations using frequentist statistics.

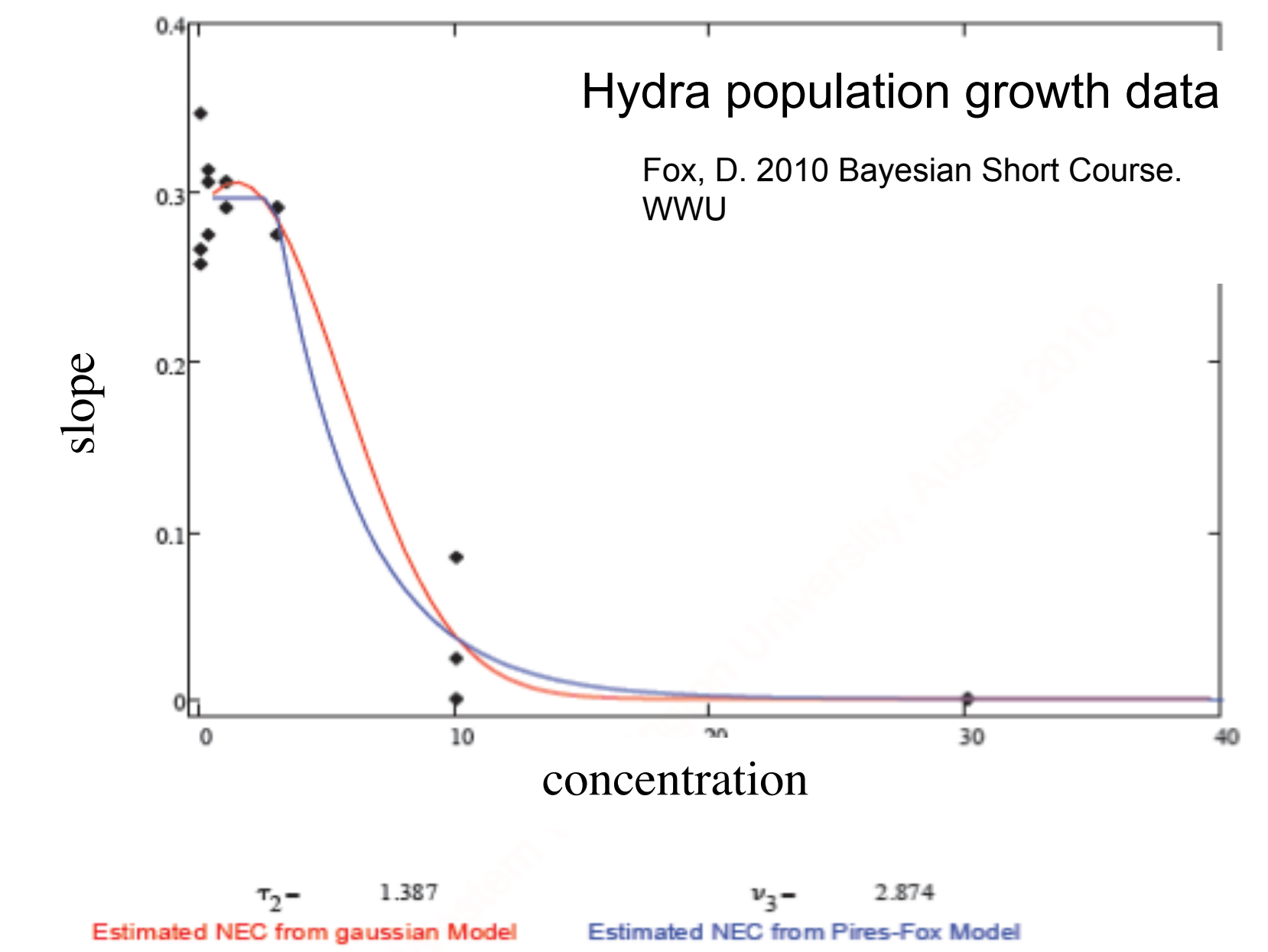
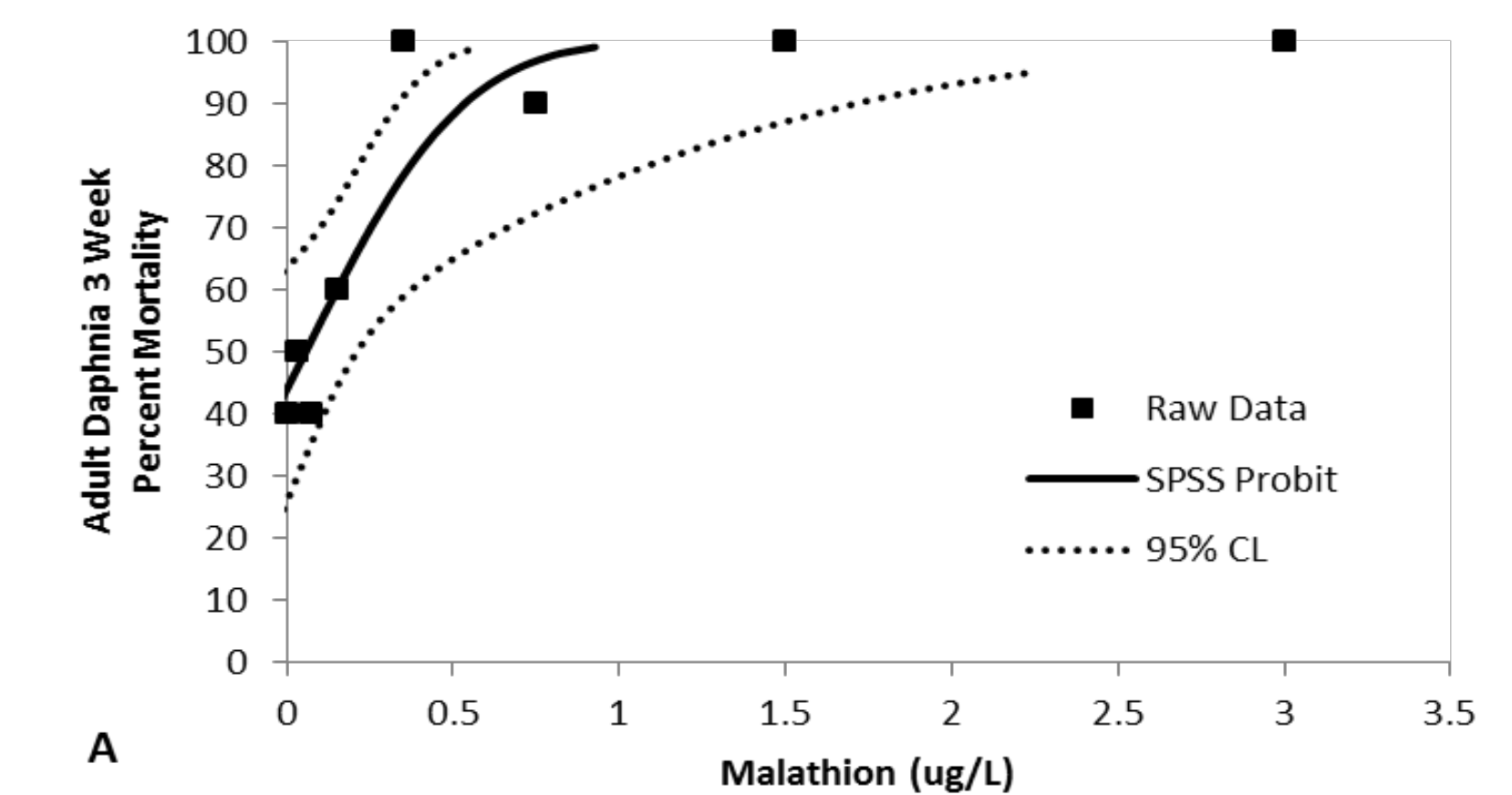
Bayesian techniques are available and have some distinct advantages.

Calculation of an NEC from curve fitting.

The ability to incorporate data from other sources-experiments.

Other papers
Fox, D.R. 2010. *Ecotoxicology and Environmental Safety*, 73: 123-131.

Wheeler, M.W., Bailer, A.J. 2009. *Risk Analysis* 29: 249-256.



As we have shown, there are no scientific or computational reasons for not using exposure-response curves as the basis for describing toxicological effects.

Given these facts, we advocate adoption of curve-fitting as the standard interpretation of laboratory test data.

Logical Consequences

To hasten the adoption of curve-fitting, we call on the Editors-in-Chief of the two SETAC journals and others to ban statistical hypothesis tests for the reporting of exposure-response.

We also call on regulatory agencies across the world to ban statistical hypothesis tests for the reporting of exposure-response from their guidance documents.

We understand that, for many toxicity tests, NOELs and LOELs are the only results that remain. However, the demonstrated uncertainties in the accurate representation of the exposure-response curves need to be acknowledged.

Work that treats NOELs and LOELs as data for further analysis, for example the derivation of species sensitivity distribution curves, should be subject to intense statistical and scientific scrutiny.

Journals, regulatory agencies and others need to require that the data from exposure-response experiments be archived into a permanent yet accessible format.

The use of Bayesian inference tools should allow the integration of datasets into more accurate depictions of exposure-response curves.

Notes and Citations

Note

A very recent editorial by Jager (2011) has suggested the banning of the reporting of the ECx from journals. He proposes that the use of a single number (the Ecx) at a single exposure time (48 or 96 hours for example) does not provide sufficient information to conduct a risk assessment with an acceptable level of uncertainty. Toxicity is certainly a process in time (Baas, Jager, Kooijman 2010) and process based models would be advantageous (Jager, Heugens, Kooijman 2006). Taking advantage of this analysis will require the generation of a number of curves each with an associated uncertainty. As risk assessors it would be great to have such relationships accurately described.

Citations

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