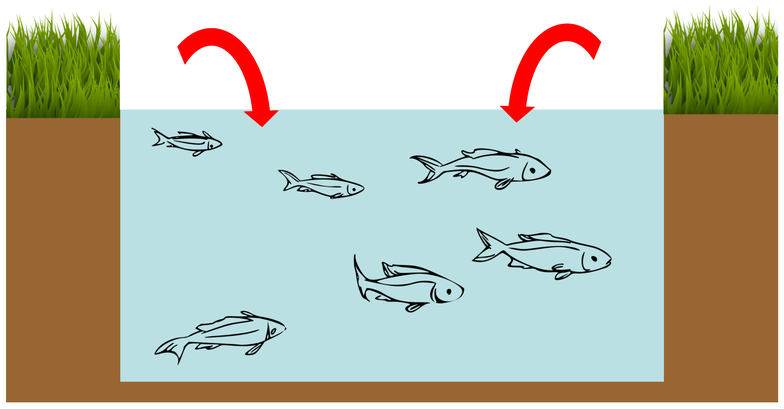
USING HISTORICAL CONTROL DATA TO CONTEXTUALISE THE VARIABILITY IN ECOTOXICITY STUDIES

Amy C. Brooks[1#], Manousos Foudoulakis[2], Hanna S. Schuster[1], & James R. Wheeler[3]

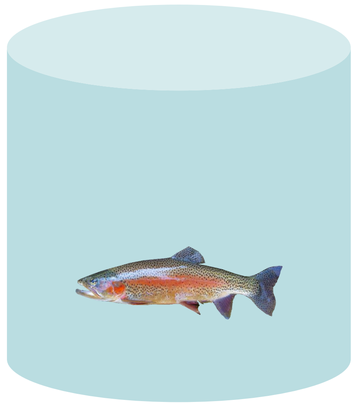
[1] Cambridge Environmental Assessments, Boxworth, UK; #Corresponding author: amy.brooks@cea-res.co.uk
[2] Corteva Agriscience™, The Agriculture Division of DowDuPont™, Halandri, Greece
[3] Present address: Shell Health, Shell International B.V. Shell Health, Carel van Bylandtlaan 16, 2596 HR The Hague, The Netherlands

1 What's the regulatory problem?

Wildlife can be exposed to chemicals from various anthropogenic sources



Risk assessments are performed to protect wildlife, estimating toxicity using standard species and methods

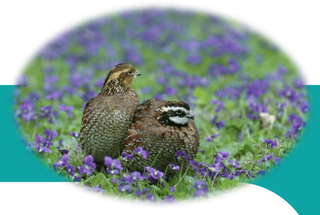


- Intrinsic and extrinsic sources of variation
- Wide range of 'normal' responses
- Determining a true treatment-related effect can be challenging
- Can be practical limitations to increasing the no. of replicates and/or dose levels
- Need for better evaluation tools to make the most of the data we can collect

2 Historical control data as a useful tool

- Historical control data (HCD) are control data compiled from similar studies, performed either before or after the concurrent study
- Can use HCD to contextualise the results from a single study
- Provides greater understanding of the test system variability and thus what constitutes a 'normal' response
- Improves the interpretation of a single study without the need for generating further data
- HCD routinely used in toxicology, being a legal requirement for toxicology of plant protection products, and clinical trials, but not in ecotoxicology
- Case studies presented here illustrating how HCD can be useful in interpreting ecotoxicology studies

Case study 1: Avian reproduction studies



- Avian repro studies investigate the effect of ~20 weeks of dietary exposure on avian reproduction; a large amount of data is collected, from egg laying through to chick survival
- A review of 32 years' worth of HCD from ~600 studies on two species was undertaken by Valverde-Garcia *et al* (2018)
- The authors calculated confidence and prediction limits for each parameter, using examples to illustrate how these could be used to interpret results from individual studies:
  - E.g. In one study, the response in the maximum dose tested appeared to be lower than the concurrent control, but the HCD clearly showed the mean to be within the realms of a 'normal' response
  - E.g. In another study, exposure to all treatment doses appeared to reduce the reproductive performance; however, the concurrent control response was unusually high and treatment means were within the realms of a 'normal' response on the basis of HCD prediction limits

Case study 2: Non-target terrestrial plants (NTTPs)

- HCD can be useful for determining what level of effect is likely to be detectable given the natural variability in the test organism's response; this was illustrated by Stavely *et al* (2018) in the context of setting suitable ER_x values for use in the NTTP risk assessment
- HCD were collated from ~100 studies on vegetative vigour (effects on emergent plants) or seedling emergence (effects on emergence and growth) across various chemical companies, CROs and active substances; minimum detectable differences and coefficients of variation were determined for the main growth parameters (shoot height/dry weight) for each species tested
- Analysis indicated no cases where an ER_5 was appropriate, and an ER_{10} was only appropriate in 12% cases; the use of ER_5/ER_{10} would require the variability in NTTP studies to be dramatically reduced; however options for this have practical limitations
- ER_{25} was reliably calculable in 82% of cases and thus more useful to consider how to incorporate this into the risk assessment to achieve the protection goals rather than using lower, unreliable ER_x estimates
- Nicely demonstrates how HCD can help translate protection goals into reliable and achievable targets

Case study 3: Mesocosms

- Control systems in mesocosms are more variable than fully controlled systems in laboratory studies; a high number of biotic/abiotic factors are interacting over time
- HCD provide invaluable information regarding seasonal dynamics and highlight which factors are key in influencing the control populations; this information can be used during data interpretation and aid decision making regarding treatment-related effects
- HCD collated from 12 studies performed at CEA (48 control reps, 18 zooplankton taxa, 5 abiotic variables) to assess the influence of abiotic factors and seasonal dynamics on zooplankton community
- HCD indicated that non-treatment related increases in pH or dissolved O_2 could reduce abundances of larger zooplankton → competitive release of smaller species → HCD useful in understanding the interaction between taxa abundance and abiotic factors to avoid misinterpretation, and can help to understand causal factors behind apparent outliers

3 Why aren't we using HCD in ecotoxicology?

"There are inherent differences between ecotox and tox data, thus HCD not relevant"
Although some differences exist in data collected (e.g. tumour incidence), HCD also collected for any parameter driving the NOEL, including those relevant for wild mammal populations.

"Using HCD may mask real effects"
The counter-argument to this is that the observed 'effects' aren't real, and the differences are just reflecting natural variability. By using HCD, we can better understand this variability, and thus interpret the results accordingly.

"There is a lack of guidance for using HCD approaches"
Guidance is needed on how to use HCD, what data to include, when it is relevant, how to compare HCD to the current study, etc. Proposals for the use of HCD in ecotox studies have been made, but need to be applied to other study types and species and formalised by organisations such as OECD, EFSA and US-EPA.

CONCLUSIONS & RECOMMENDATIONS

- HCD can be useful in contextualising results from single studies and in determining what level of effect may be most meaningful for a given parameter in a test system.
- Understanding HCD can lead to improvement of test designs, better linkage of laboratory results/interpretation to the protection goals, make the best use of all available data and avoid unnecessary additional data generation (particularly for vertebrates) or the need for extensive higher tier risk assessments.
- **We encourage organisations such as OECD, EFSA and US-EPA to develop guidance on the principles of historical data collection, reporting, statistical analysis and interpretation to aid and encourage the use of these valuable data in ecotoxicity study design and interpretation.**
- **A more detailed review of this topic can be found in the recent open-access paper by Brooks *et al* (2019)**

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