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New designs and evaluation of in-vitro bioassays in regulatory toxicology

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In 2023, the 2nd FDA Modernisation Act proposes that in-vivo data will no longer be required for drug registration. Therefore, more in vitro bioassays will be used for the final positive/negative decision matrix in RegTox. The definition of 'randomised unit' (RU) is central - as the animal following the 'rat-is-a-little-human' paradigm is no longer applicable. Whether plate/run/cell culture/assay is defined as RU has a serious impact on the false positive/false negative decision rate ratio. Furthermore, different mixed effects models are appropriate for both simple 'concentration vs. control' comparisons and for benchmark dose estimation (to be precise: the lower confidence limit of BMD). A real data example is used to discuss both the underlying design issues and the evaluation process. Relevant CRAN packages will be used. The conclusions are: i) this is a relevant issue in RegTox, ii) new approaches to both design and analysis are needed, e.g. sample size estimation for Dunnett-type procedures in mixed effect models, iii) the definition of relevant effect sizes for both hypothesis testing and model-based estimates (such as BMD) is needed, and iv) the information from historical control data should be used.