On validation of micronucleus tests using historical controls

Jonathan Rathjens[*1], Verena Ziegler[2] and Hannes-Friedrich Ulbrich[3]

[1]Early Development Statistics, Chrestos Concept GmbH & Co. KG, Essen, Germany
[2]Genetic & Computational Toxicology, Bayer AG, Berlin, Germany
[3]Research & Pre-Clinical Statistics, Bayer AG, Berlin, Germany

Herbstworkshop AG Non-Clinical Statistics, IBS-DR

16/17 November 2023

Abstract

Background: In-vitro micronucleus tests (MNT) are used as a routine method to assess genotoxicity. Distribution parameters of control groups' measurements are observed over time to ensure validity of results. It is checked whether the observations from control groups in a new experiment fit to the respective ranges calculated from historical data. Guidelines on assay validation refer to both negative (solvent) and positive controls.

Data: We consider data from solvent control (dimethylsulfoxide, DMSO) and positive control groups from about 15–20 historical MNT experiments with each of three positive control substances (mitomycin C, cyclophosphamide, vinblastine sulfate salt). One experiment includes six samples per group. We focus on the relative micronucleus count as principal outcome when evaluating genotoxicity.

Methods: As the data are relative quantities and strictly positive, they are assumed to be lognormally distributed, considered on log-scale, and aggregated by the geometric mean. This multiplicative approach is also consistent with expressing groups' relations as ratios, which can be used to quantify the width of the 'separation band'. Control ranges are derived in form of prediction intervals for the groups' means. We emphasize that we model the positive control data in a similar way to the negatives. Historical experiments are retrospectively cross-validated.

Results: Changes between experiments turn out to be nearly parallel in the solvent and the positive control group, with some exceptions. Variability between experiments appears to be greater than within. Some experiments are outside the control ranges regarding one of the groups.

Perspectives: Joint modeling of data from a series of subsequent experiments can include a temporal correlation structure. But also non-stationarity, especially a drift in the groups' means, is possible and should be accounted for when validating a new experiment.

---

[*]jonathan.rathjens@chrestos.de