

How to set historical control limits using the R package „predint“

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Short bio

12/2026 - 12/2021: PhD Student at the Department of Biostatistics of the LUH.
Topic of PhD thesis: Prediction intervals based on historical control data obtained from bioassays
since 01/2022: PostDoc at the Department of Biostatistics of the LUH
Research topics: Historical control data and their application, bootstrap calibration, statistical intervals (mainly prediction and tolerance intervals)

Abstract

For reporting toxicology studies, the presentation of historical control data (HCD) and the validation of the concurrent control group using historical control limits (HCL) have become requirements. However, many regulatory guidelines fail to define *how* such limits should be calculated. Hence, several inappropriate heuristics such as the historical range or confidence intervals for the historical mean are used by the toxicological community for the calculation of HCL.

Anyhow, since it is consensus that the desired HCL should cover the observations from the concurrent control with 95% of confidence, several authors emphasize the application of prediction intervals for the calculation of HCL^{1,2,3}. Furthermore, it seems that also the EFSA favors the application of prediction intervals over other methodology⁴.

Hence, in the current talk a user friendly way for the computation of prediction intervals will be shown using the R package „predint“. This package enables the calculation of prediction intervals for overdispersed binomial endpoints (e.g. as in carcinogenicity assays), overdispersed counted endpoints (e.g. as in the Ames test) or continuous endpoints that are modeled based on random effects models (e.g. as in the comet assay). The calculation of prediction intervals that are in line with the requirements of certain OECD guidelines will be shown based on real life data.

References

- 1) Menssen M. (2023): The calculation of historical control limits in toxicology: Do's, don'ts and open issues from a statistical perspective. *Mutation Research - Genetic Toxicology and Environmental Mutagenesis* 892:503695
- 2) Dertinger et al. (2023): Assessing the quality and making appropriate use of historical negative control data: A report of the International Workshop on Genotoxicity Testing (IWGT). *Environmental and Molecular Mutagenesis* 1–22
- 3) Kluxen et al. (2021): Using historical control data in bioassays for regulatory toxicology. *Regulatory Toxicology and Pharmacology* 125:105024
- 4) EFSA (2024): Draft Scientific Opinion on the use and reporting of historical control data for regulatory studies. Public Consultation PC-0856