Institute of Cell Biology and Biophysics

Leibniz Universität Hannover

The use of (historical) control data in toxicology

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Outline

1) Historical control data (HCD)

- Definition
- Overview about applications
- Basic assumptions

2) Historical control limits

- Background (guidelines)
- Aim
- Coverage probability
- Real life example

3) Conclusions

Historical control data (HCD)

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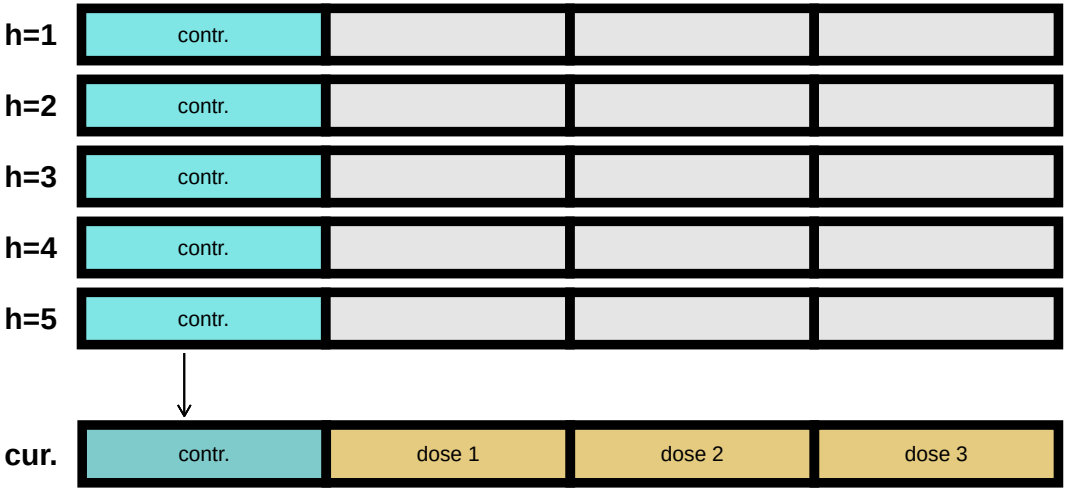
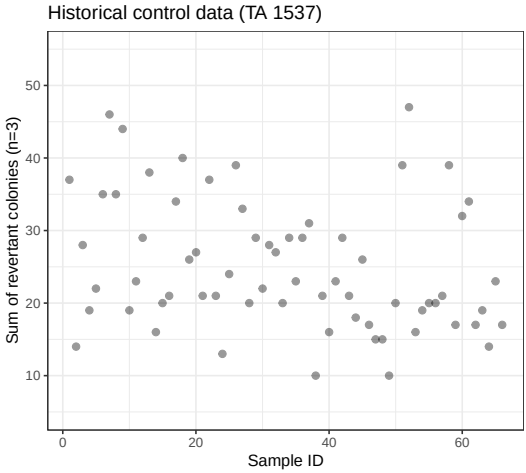
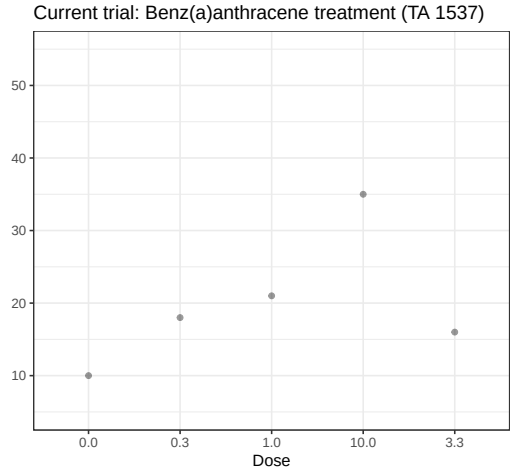


Historical control data (HCD)





[1] **Tarone 1982:** The use of historical control information in testing for a trend in Poisson means, Biometrics 38:457-462.

Historical control data (HCD)

Does it matter in pre-clinical research?

- Coja et al. 2022
  - At least 63 recent OECD test guidelines refer to the use of historical control data
  - At least 186 publications with a relevant reference to the use of HCD in toxicology published since 1980
- Menssen 2023
  - Web of Science July 2023
  - topics “historical control data” and “toxicology”
  - 143 publications published between 1991 and 2023
- Relatively few methodological papers

[1] **Coja et al. 2022:** Preparatory work on how to report, use and interpret historical control data in (eco)toxicity studies. EFSA supporting publication EFSA Supporting Publication 19(9):EN-7558, **Menssen 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

Historical control data (HCD)

Does it matter in pre-clinical research?

- Several recent papers
  - Kluxen et al. 2021
  - Deringer et al. 2023
  - Menssen 2023

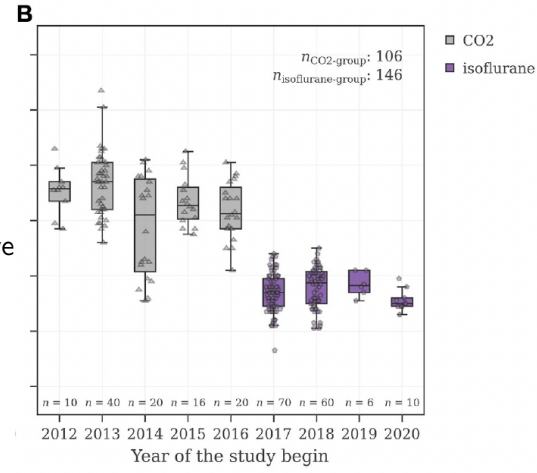
- eTransafe
  - Industry led project
  - Gather HCD from several companies

[1] **Kluxen et al. 2021:** Using historical control data in bioassays for regulatory toxicology, Regulatory Toxicology and Pharmacology 125:105024; **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; **Menssen 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; **Sanz et al. 2021:** eTRANSAFE: data science to empower translational safety assessment, Nature Reviews Drug Discovery 22:605-606

Historical control data (HCD)

Assumption

- HCD and current observation(s) derive from the **same** data generating process



Source: Gurjanov et al. 2023[1]

[1] **Gurjanov et al. 2023**: Hurdles and signposts on the road to virtual control groups — A case study illustrating the influence of anesthesia protocols on electrolyte levels in rats. Front. Pharmacol. 14:1142534

Applications

	Aim	Clinical	Pre-clinical
MAP	Reduce individuals in ccg	yes	no (yes)
Virtual control groups	Reduce individuals in ccg	yes	no (yes)
Inclusion in test	Enhance power	no (yes)	no (yes)
Control limits	Validate ccg	no	yes

[1] **Walley et al. 2016**: (2016) Using Bayesian analysis in repeated preclinical in vivo studies for a more effective use of animals. Pharmaceut. Statist. 15:277–285 **Gurjanov et al. 2023**: Hurdles and signposts on the road to virtual control groups — A case study illustrating the influence of anesthesia protocols on electrolyte levels in rats. Front. Pharmacol. 14:1142534. **Tarone 1982:** The use of historical control information in testing for a trend in Poisson means, Biometrics 38:457-462. **Tarone 1982:** The use of historical control information in testing for a trend in proportions, Biometrics 38:215-220. **Kitsche et al. 2012:** The use of historical controls in estimating simultaneous confidence intervals for comparisons against a concurrent control, Computational Statistics and Data Analysis 56(12):3865-3875

Historical control limits

Historical control limits

OECD 471, 473, 490:

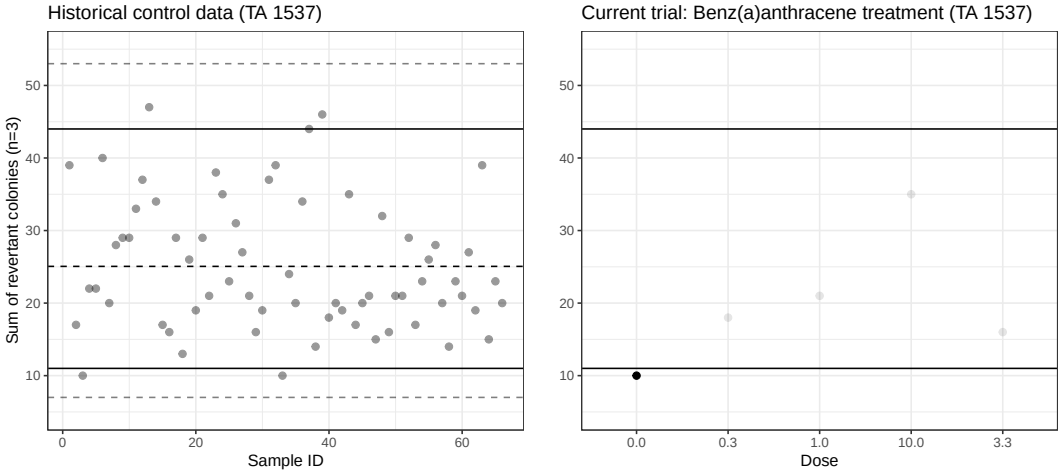
- . . . concurrent negative controls should ideally be within the [historical] 95% control limits of that distribution
- . . . historical negative control data with ranges, means and standard deviations

OECD 2016

- . . . . using quality control charts to assess the historical control databases and to show that the methodology is "under control" in the individual laboratories. . .

[1] **OECD 471:** Bacterial Reverse Mutation Test; **OECD 473:** In Vitro Mammalian Chromosomal Aberration Test; **OECD 490:** In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene; **OECD 2016:** Overview of the set of OECD genetic toxicology test guidelines and updates performed in 2014–2015

Historical control limits



[1] **Tarone 1982:** The use of historical control information in testing for a trend in Poisson means, Biometrics 38:457-462.

Historical control limits

Aim

- Estimate limits that cover the central x% of the underlying distribution

Assumption

- All observations derive from the **same** data generating process

[1] **Menssen 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

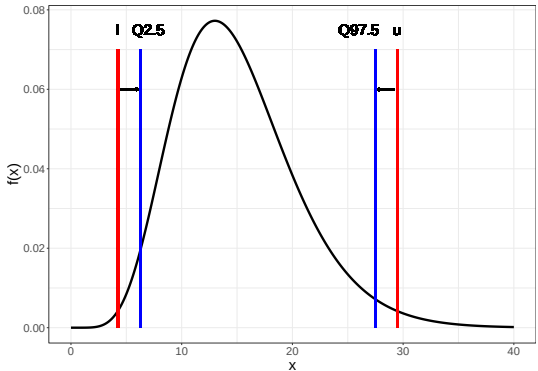
Historical control limits

Coverage probability

- $P(l \leq y^* \leq u) = 1 - \alpha$

Equal tail probabilities

- $P(l \leq y^*) = 1 - \alpha/2$
- $P(y^* \leq u) = 1 - \alpha/2$



Historical control limits

Confidence intervals

- $P(l \leq \theta \leq u) = 1 - \alpha$
- Cover a model parameter θ

Prediction intervals

- $P(l \leq y^* \leq u) = 1 - \alpha$
- Cover the central x% of the distribution

Tolerance intervals

- $P(P(l \leq y^* \leq u) \geq \beta) = \gamma = 1 - \alpha$
- "Confidence interval" for the central x% of the distribution

Historical control limits

OECD 471, 473, 490:

- . . . concurrent negative controls should ideally be within the [historical] 95% control limits of that distribution

Prediction intervals

- $P(l \leq y^* \leq u) = 1 - \alpha$
- Cover the central x% of the distribution

Historical control limits

Hierarchical design of HCD

- Certain experimental units nested within certain hist. control
- Between study variance vs. within study variance

Continous data

- Hierarchical mixed or random effects models

Dichotomous or count data

- Hierarchical generalized mixed or random effects model
- Generalized linear model with between-study overdispersion

Historical control limits

The R package 'predint'

```r
# Install the package from CRAN
install.packages("predint")

# Install developmental version
devtools::install_github("MaxMenssen/predint")

# Load the package to current R session
library(predint)
```

- Prediction intervals based on random effects models
- Prediction intervals for overdispersed binomial data
- Prediction intervals for overdispersed Poisson data

Application

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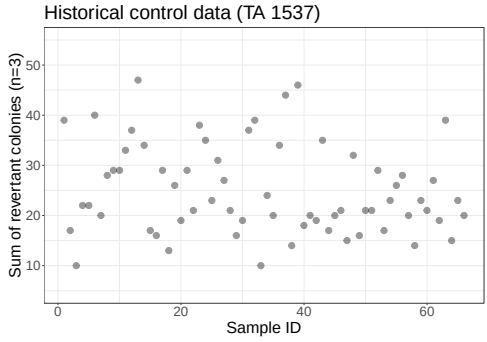
Count data

- Quasi-Poisson assumption
- Between-study overdispersion

$$E(Y_h) = n_h\lambda$$
$$var(Y_h) = \phi n_h\lambda$$
$$\phi > 1$$

- (Over)dispersion parameter ϕ



Application (heuristics)

Sheward c-chart

- $\bar{y} \pm k\sqrt{\bar{y}}$
- Poisson assumption

Mean $\pm$ k standard deviations

- $\bar{y} \pm k\sqrt{\hat{\sigma}^2}$
- Overdispersion possible

Disadvantages

- Ignore variability of estimates
- No equal tail Probabilities

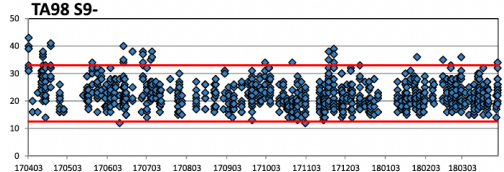


Fig. 1 of Levy et al. 2019 (adapted)

[1] **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), **Levy et al. 2019**: Recommended criteria for the evaluation of bacterial mutagenicity data (Ames test)

Application (prediction intervals)

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Wald-type prediction interval

$$[l, u] = \hat{y}^* \pm z_{1-\alpha/2}\sqrt{\widehat{var}(\hat{y}^*) + \widehat{var}(Y)}$$

$$[l, u] = n^*\hat{\lambda} \pm z_{1-\alpha/2}\sqrt{\frac{n^{*2}\hat{\phi}\hat{\lambda}}{\bar{n}H} + n^*\hat{\phi}\hat{\lambda}}$$

- Uncertainty of the estimates is taken into account
- Still symmetrical

Remedy

- Bootstrap calibration

Aim

- Substitute $z_{1-\alpha/2}$ by q_l and q_u
- Enable equal tail probabilities

```
library(predint)
q_vec <- bisection(y_star_hat,
                   pred_se,
                   y_star)
```

[1] **Menssen et al. 2024**: Prediction intervals for overdispersed Poisson data and their application in medical and pre-clinical quality control, under review in Pharmaceutical Statistics

Application (prediction intervals)

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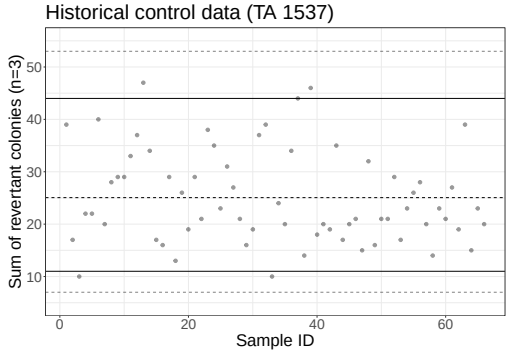
Quasi-Poisson assumption

$$\Big[l = n^*\hat{\lambda} - q_l\sqrt{\frac{n^{*2}\hat{\phi}\hat{\lambda}}{\bar{n}H} + n^*\hat{\phi}\hat{\lambda}}$$

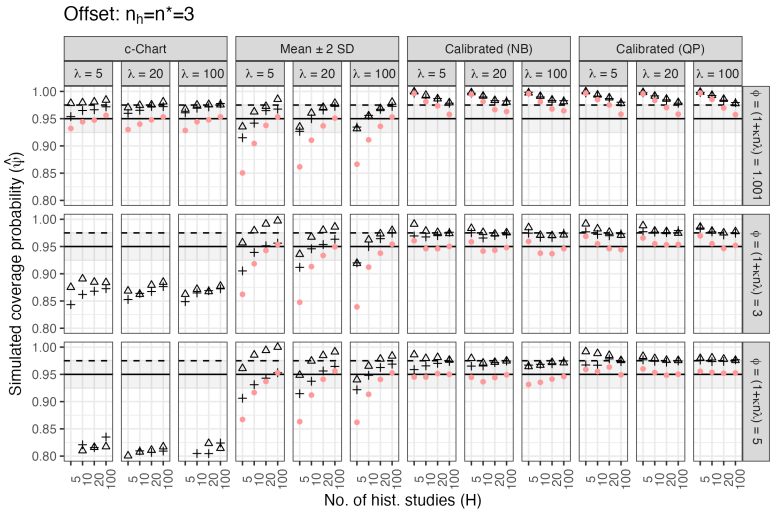
$$u = n^*\hat{\lambda} + q_u\sqrt{\frac{n^{*2}\hat{\phi}\hat{\lambda}}{\bar{n}H} + n^*\hat{\phi}\hat{\lambda}}\Big]$$




```
library(predint)
pred_int <- quasi_pois_pi(histdat = tarone_hcd, newoffset=3)
```

[1] **Menssen et al. 2024**: Prediction intervals for overdispersed Poisson data and their application in medical and pre-clinical quality control, under review in Pharmaceutical Statistics

Application (coverage probabilities)



[1] **Menssen et al. 2024**: Prediction intervals for overdispersed Poisson data and their application in medical and pre-clinical quality control, under review in Pharmaceutical Statistics

Conclusions

Conclusions

Historical control limits

- Informal comparison preferred in pre-clinical research
  - No guidance in guidelines
  - Several inappropriate heuristics in use
  - Prediction intervals available via `predint`

Formal use of HCD

- High potential for application of
  - MAP
  - Virtual controls
  - Direct inclusion in test procedure

Conclusions

- Several open issues
- High potential for interdisciplinary research
- Platform for knowledge exchange is needed

EFSA Call

EFSA Call for public consultations

- Draft: Scientific Opinion on the use and reporting of historical control data for regulatory studies
- Open for public consultation
- Dedline 29.04.2024

Thank you!