Variability of chronic rodent bioassays

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Content

Rodent Carcinogenicity E Gottmann, S Kramer, B Pfahringer and C Helma
Data quality in predictive toxicology: reproducibility of rodent carcinogenicity experiments
Environ Health Perspect 109:509–514 (2001)
https://doi.org/10.1289/ehp.01109509

Lowest observed adverse effect level (LOAEL) C Helma, D Vorgrimmler, D Gebele, M Gütlein, B Engeli, J Zarn, B Schilter and E Lo Piparo
Modeling Chronic Toxicity: A Comparison of Experimental Variability With (Q)SAR/Read-Across Predictions
Front Pharmacol 9 (2018)
https://doi.org/10.3389/fphar.2018.00413

Carcinogenicity Data

- Carcinogenic Potency Database(CPDB, Gold 1997)
- 1,289 unique compounds
- 2 Subsets
  - National Toxicology Program (NTP)
  - General literature
- 121 common compounds in both subsets

Carcinogenicity Classification

- **57%** concordant classifications (69/121 compounds, 39 carcinogens, 30 non-carcinogens)

  Rats 62% concordant classifications
  Mice 49% concordant classifications
  Multi species carcinogens 58% concordant classifications
  Multi organ carcinogens: 52% concordant classifications

- poor reproducibility of sex, species and organ specific effects

Carcinogenicity TD50's

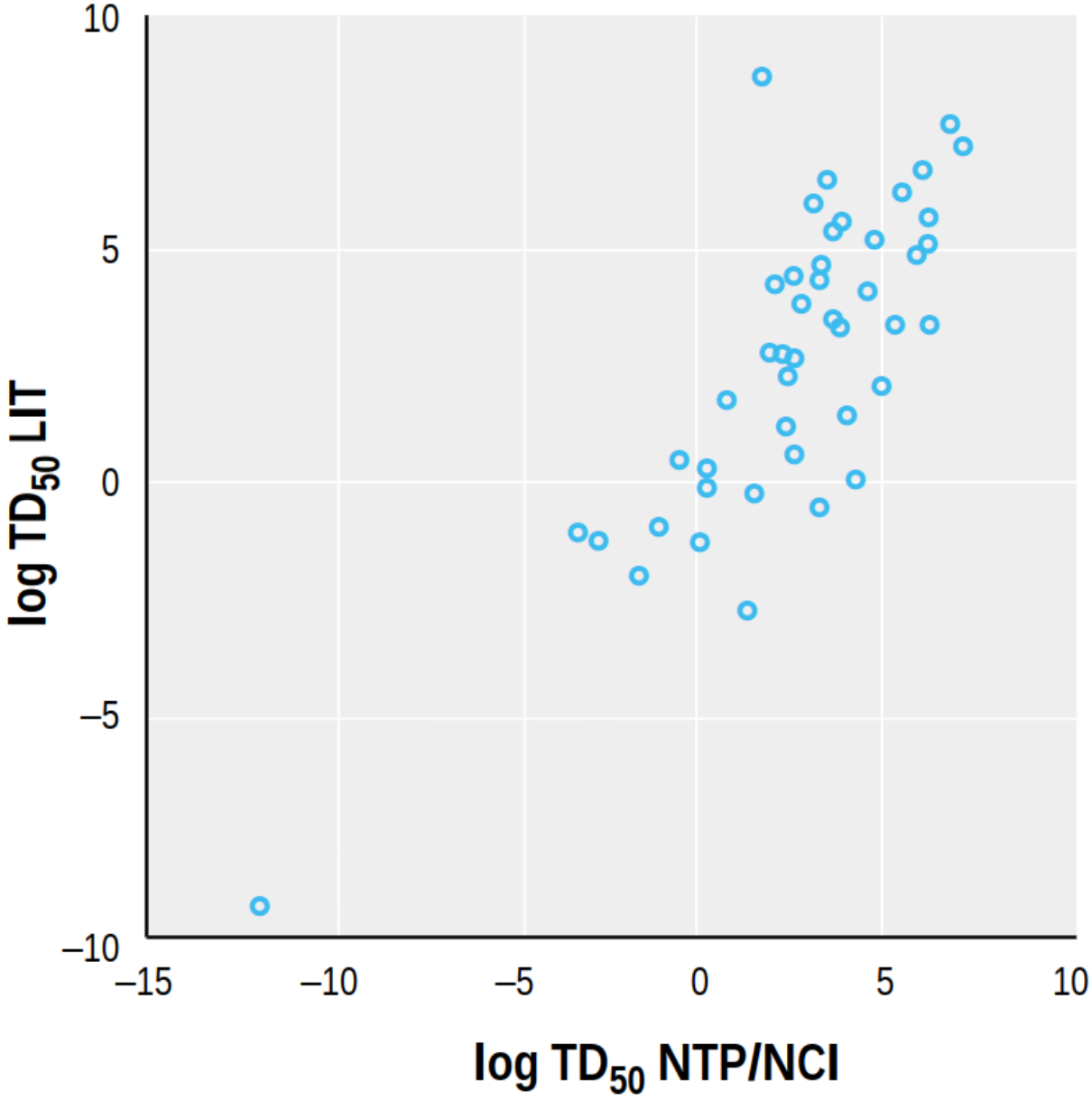


Figure 2. Correlation of carcinogenicity TD_{50} values from the NTP/NCI and the literature (LIT) part of the

Carcinogenicity caveats

- low sample size
- no standardized protocols for literature data

Gold et al. (1987)

- 38 compounds from the literature
- 93% reproducibility for rats
- 76% for mice
- 34 studies were published by the same authors (!)

LOAEL Data

Chronic (>180 days) lowest observed effect levels (LOAEL) for rats (Rattus norvegicus) after oral (gavage, diet, drinking water) administration

Nestlé Database 567 LOAEL values for 445 unique chemical structures from the literature (Mazzatorta et al., 2008)

Swiss Food Safety and Veterinary Office (FSVO) Database 493 rat LOAEL values for 381 unique chemical structures from pesticide evaluations (Zarn et al., 2011, 2013)

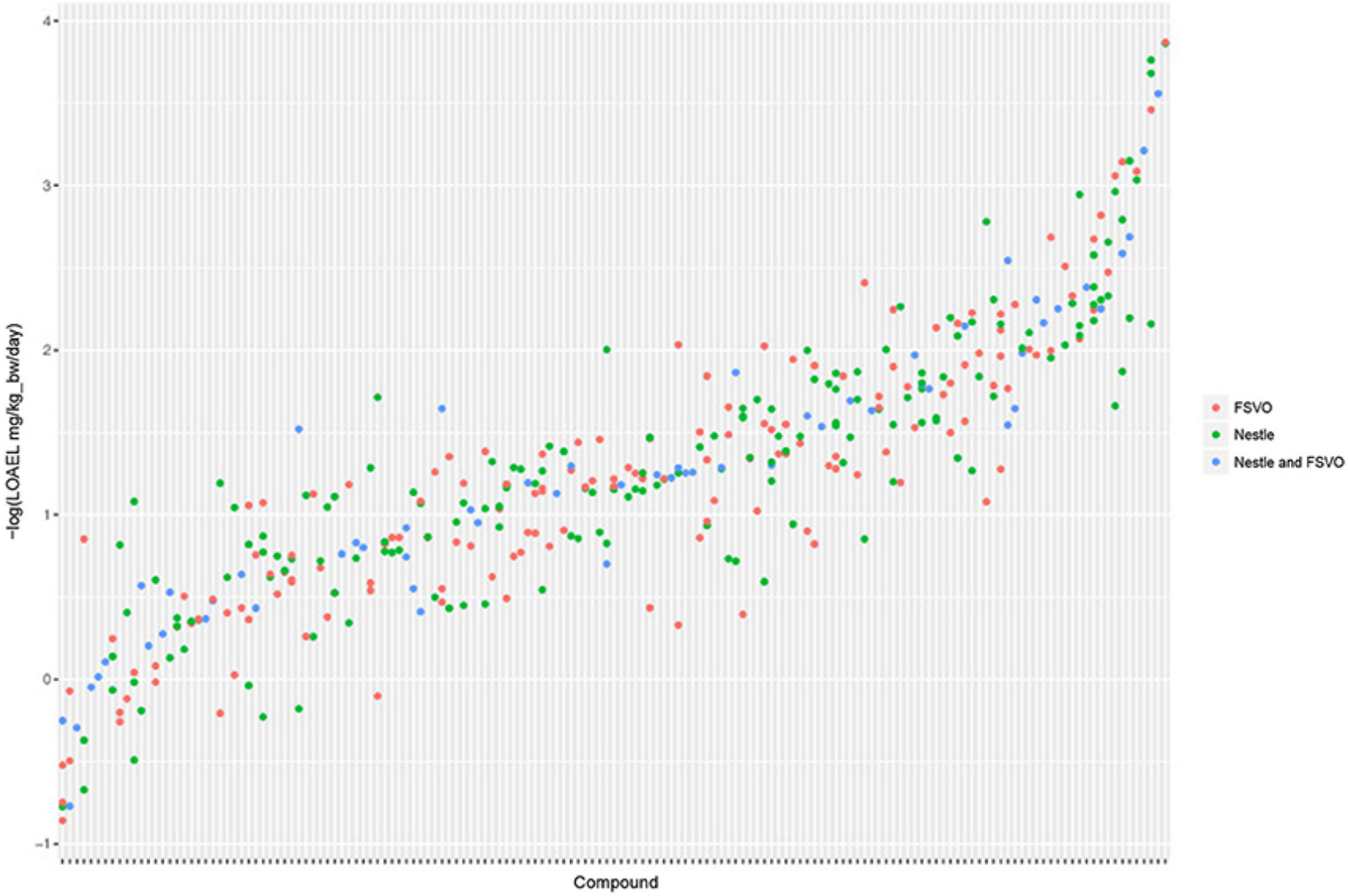
- European Food Safety Authority (EFSA) (EFSA, 2014)
- Joint FAO/WHO Meeting on Pesticide Residues (JMPR) (WHO, 2011)
- US EPA (US EPA, 2011)

Combined dataset

- compounds that occur in both databases
- 375 LOAEL values for 155 unique chemical

LOAEL Variability

Both datasets contain substances with multiple measurements



All datasets have almost the same experimental variability (standard

LOAEL Correlation

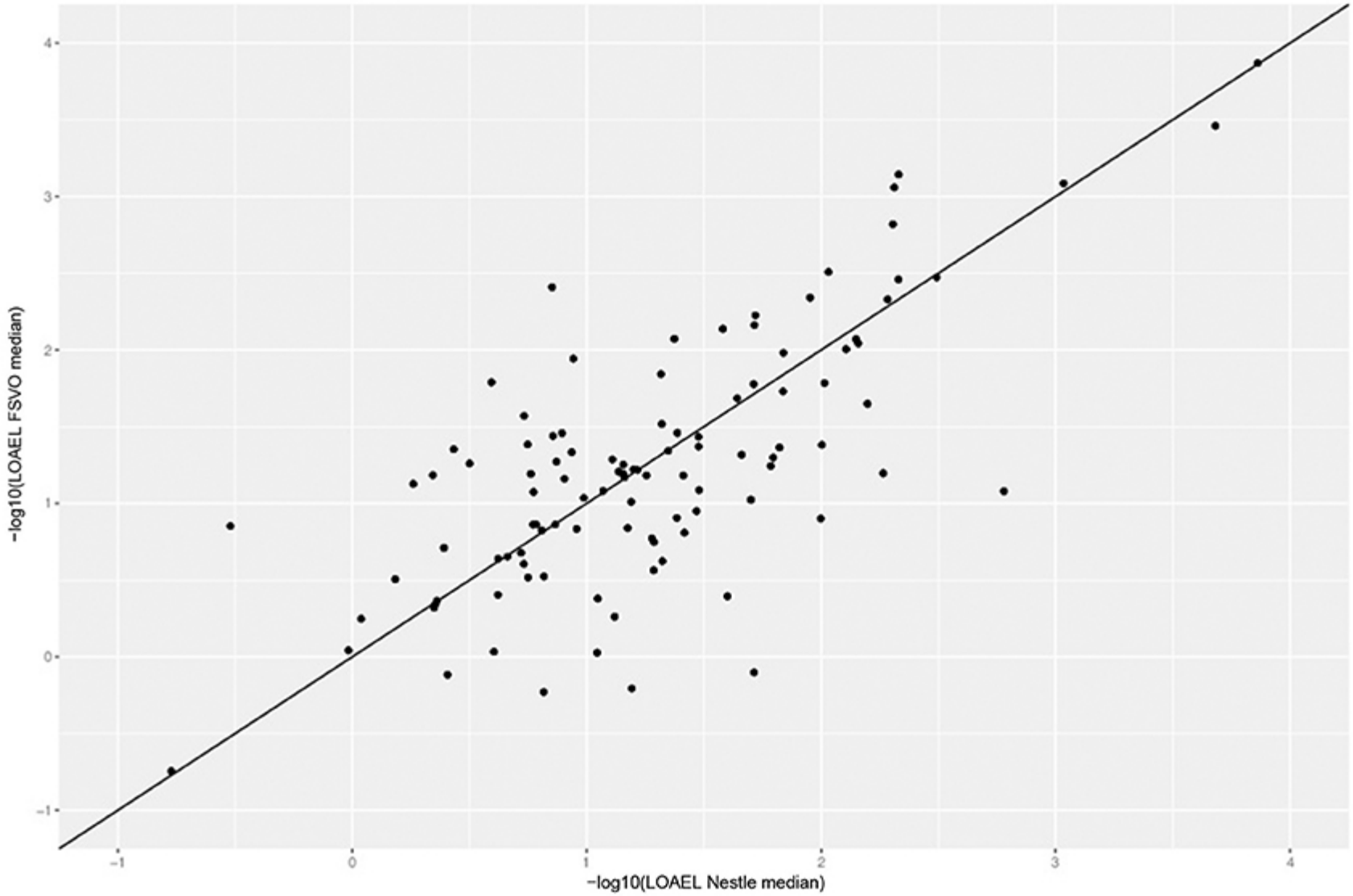
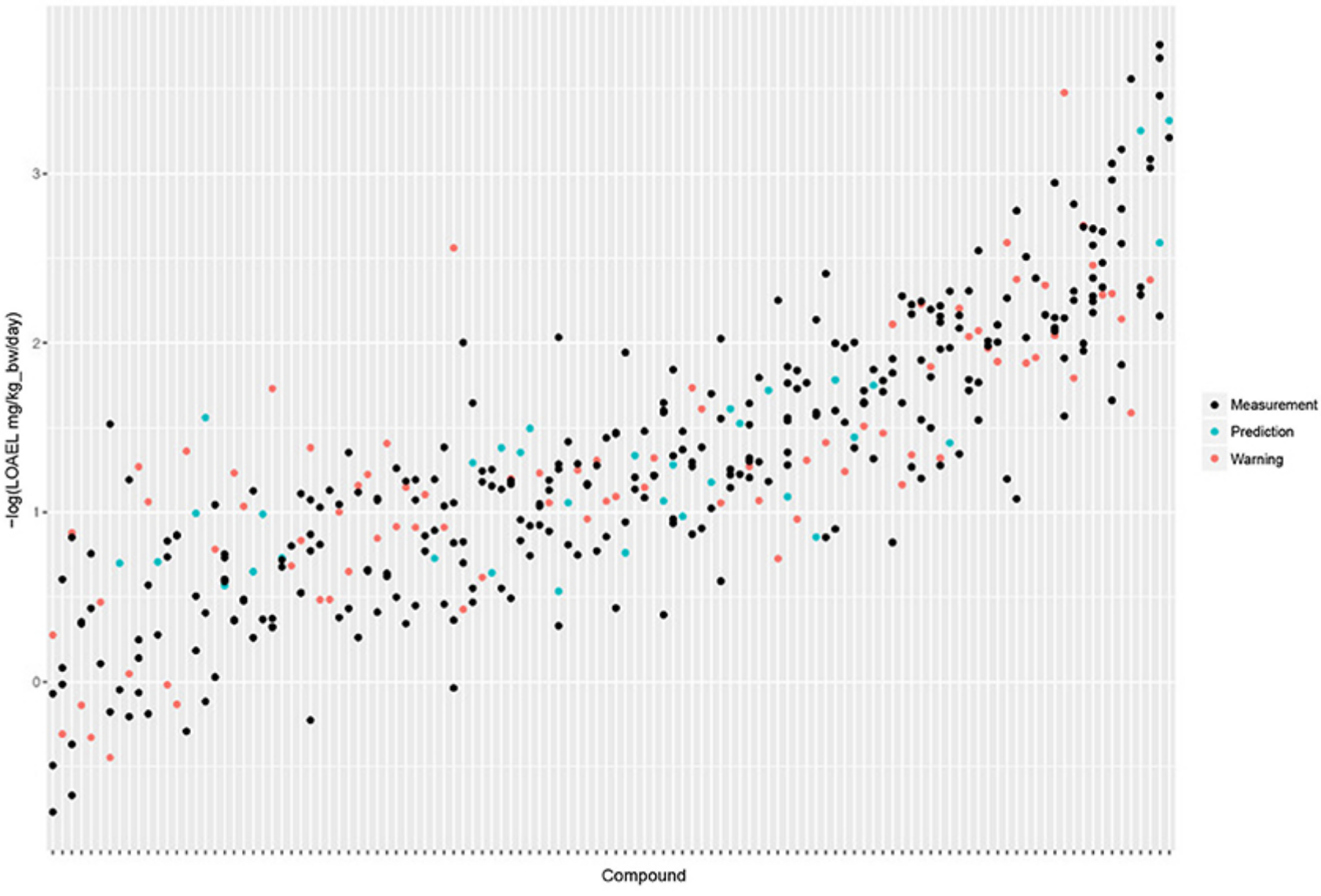


Figure 1: r^2: 0.52, RMSE: 0.59, p-value $<$ 2.2e-16

As both databases contain duplicates medians were used for the

LOAEL Experiments vs Predictions



Conclusions

- Carcinogenicity classifications seem to be poorly reproducible (57% concordant classifications for repeated experiments)
- Experimental LOAEL values have a variablity of approximately 1.5 log units (orders of magnitude)
- Variability in chronic *in vivo* bioassays might be caused by
  - biological complexity
  - long term experimental conditions
  - evaluation complexity
  - statistical limitations (low number of animals/treatment)
- Good *in-silico* models have the same accuracy as biological experiments (*in-vivo* and *in-vitro*) for **compounds in their applicability domain**

https://in-silico.ch/presentations/epa-nam-2022/