The Impact of Study Inclusion Criteria on the Determination of Point of Departure Methods in the Carcinogenicity Potency (CPDB) Database

Bryan Hobocienski[1], João Vinícius Ribiero[1], James Rathman[1,3], Chihae Yang[1,2] , Aleksandra Mostrag[1], Tomasz Magdziarz[2],

[1] MN-AM, Columbus, OH, USA; [2]MN-AM, Nurnberg Germany; [3]The Ohio State University, Columbus, OH, USA

1 INTRODUCTION

BACKGROUND

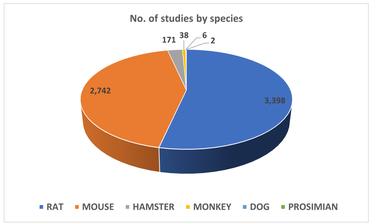
- The carcinogenicity potency (CPDB) database has been constructed over three decades (1980-2004) and contributed significantly to the establish the Threshold of Regulation (TOR) program at US FDA CFSAN (CFR21).[1,2]
- The database has been recently updated with improved study inclusion criteria including 43 new test substances from over 100 new studies (US NTP and EFSA).
- In addition to the dose-level tumor observations, the original database also provides a potency measure based on toxic dose, namely TD50, the dose at which 50% of the animals are expected to have tumors. The use of TD50 has been controversial.
- Concerns were raised during the update due to a lack of transparency and reproducibility of the TD50 approach. Potency is critical in preparing a TOR dataset or to derive a cancer threshold for Threshold of Toxicological Concern.

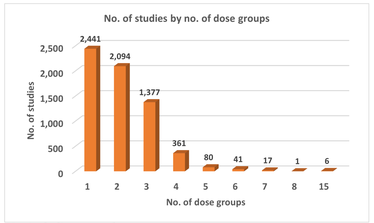
OBJECTIVES OF THIS STUDY

- Update the TOR dataset.
- Adopt the benchmark dose (BMD) modeling strategy to address transparency and reproducibility concerns.
- Apply a new set of inclusion criteria when calculating the BMDL/BMD.
- Use software programs and guidelines endorsed by regulatory agencies.

2 CPDB DATABASE

- The graphs below summarize the content of the CPDB database provides 1,593 test substances for 6,357 oral rodent bioassays.
- 1,015 compounds have studies where the number of dose groups exceeds 1.



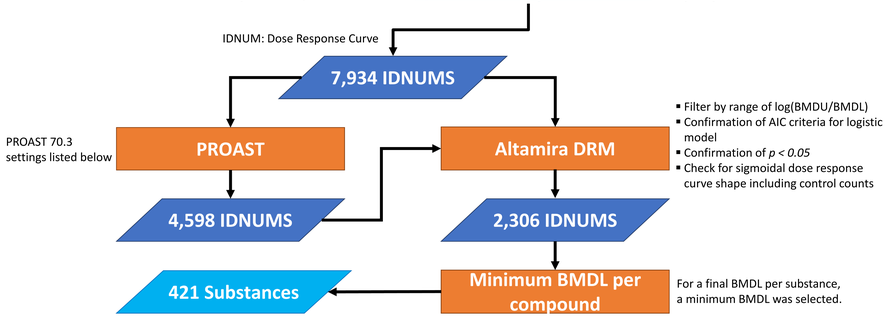


Not including control groups

3 METHODOLOGY

INITIAL DATASET PREPARATION[3]

- Studies from which dose-response data sets are derived must include:
  - ❑ at least 2 dose groups excluding control
  - ❑ no mixed tumor types or sites
  - ❑ control information
- Further evaluations considered for the following cases:
  - ❑ non-human related findings
  - ❑ clearly negative observations
  - ❑ no evaluation decision due to inadequate experiment by NTP
- From this process, a dataset of **7,934 dose response curves** are prepared



DOSE-RESPONSE MODELING SOFTWARE

- PROAST 70.3 (RIVM) was used to estimate the BMDL/BMD/BMDU
  - ❑ Single chemical: PROAST Web (https://proastweb.rivm.nl/)
  - ❑ Batch mode: PROAST R package (https://www.rivm.nl/en/proast)
- PROAST configuration
  - ❑ BMR (Benchmark Response): 0.10
  - ❑ Risk type: additional risk
  - ❑ Constraint on steepness parameter: 0.01
  - ❑ Critical AIC (Akaike Information Criteria) value[4]:

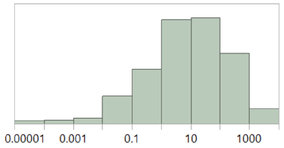
$$AIC_{model} = 2(\#\ parameters) - 2ln(likelihood) < AIC_{full} + 2$$

  - ❑ Approach for calculating BMD confidence interval: model averaging, bootstrap 200
  - ❑ List of models considered: null, full, two-stage, log-logistic, Weibul, log-probit, gamma, LVM:Exponential, LVM:Hill
- Altamira Dose-Response Model (DRM)
  - ❑ Batch mode models to confirm and further refine external results by applying additional user criteria (see above)

4 RESULTS

FINAL TOR DATASET

A final tumor dataset of 421 substances containing BMDL, BMD, and BMDU values at BMR10 was established.



Histogram of BMDL10

Statistical Summary of 421 BMDL10 values in the CPDB database

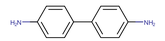
N: 421
Mean: 150.9

Quantiles

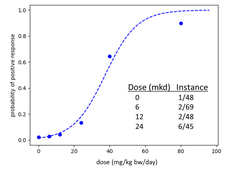
100.0%	maximum	6390
75.0%	quartile	75.65
50.0%	median	9.85
25.0%	quartile	1.22
10.0%		0.1428
0.0%	minimum	0.0000199

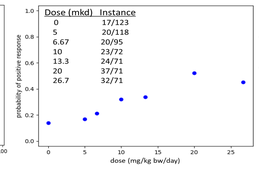
EXTREME EXAMPLES

Dose Response Curves of Benzidine



The dose response curve meets all the requirements of the modeling specifications.

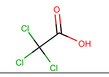




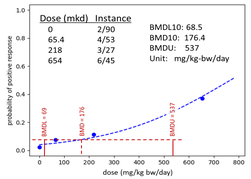
- Weakly dose-related (transient at higher dose)
- High counts in the control group

LITERATURE COMPARISONS

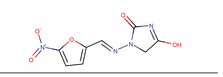
❑ Trichloroacetic Acid (TCA)[5]



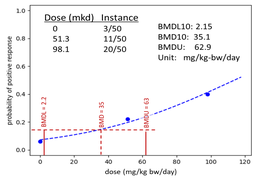
- Mouse [F], B6C3F1, 82 week, Oral-drinking water
- BMDL10 comparison
  - This study: BMDL=68.5 mg/kg-bw/day for hepatocellular adenoma
  - US EPA: 4.64 mg/kg-bw/day (using BMDS) for hepatocellular adenoma/carcinoma not clear



❑ Nitrofurantoin



- Rat [M], Fischer344, 105 week, Oral-dietary
- BMDL10 comparison
  - This Study: BMDL=2.15 mg/kg-bw/day for kidney tubular adenoma/carcinoma
  - EFSA: 61 mg/kg-bw/day (using PROAST) for osteosarcoma (kidney effect was not mentioned)



5 CONCLUSION

- A set of transparent study inclusion criteria has been developed and applied to the CPDB database systematically.
- Benchmark Dose modeling strategies have been applied and demonstrated the reproducible batch operations.
- A set of 421 substances with BMDL10, BMD10, and BMDU10 values have been established. This dataset can support risk assessment approaches involved in TOR and Threshold of Toxicological Concerns.

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Contacts: james.rathman@mn-am.com, chihae.yang@mn-am.com