Cancer Dose-Response Data Collection and Cleansing

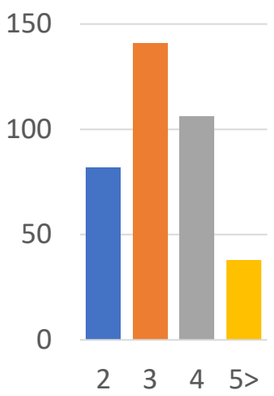
Data Collection

- 880 Toxicity values and study information – Wignall et al. (2014)
- 3,064 Toxicity values and study information – Wignall et al. (2018)

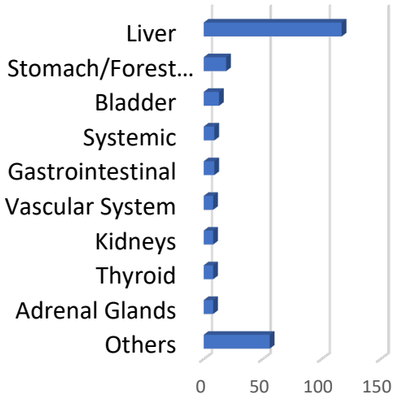
Data Cleaning - 255 Caner slope factors (CSFs)

- At least 3 dose-response (D-R) data points
- Oral administration only

No. of D-R data points



Cancer Organ Types



Bayesian Benchmark Dose (BBMD) Modeling and Probabilistic Extrapolations

Likelihood | D-R Data | Prior | 8 Models

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Markov Chain Monte Carlo Sampling – 5,000 Iterations

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Posterior Distributions (BBMD)

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Model Comparison to Traditional Approaches

Data

Benchmark Dose Software (BMDS) + Traditional method

BMDS → BMDS $BMDL_{10}$ → × DAF → BMDS HED → 0.1/HED → BMDS CSF

BBMD with Model Averaging (MA) + Traditional method

BBMD → MA $BMDL_{10}$ → × DAF → MA HED → 0.1/HED → MA CSF

Probabilistic BBMD + Probabilistic method

BBMD → Prob. $BMDL_{10}$ → Probabilistic Inter-/Intra-Species Extrapolation → Prob. CSF

Population and Individual Risk Estimation And Uncertainty Contribution Characterization

Population Risk Estimation

- Risk-Specific Dose (RSD): dose causing a specific extra risk of cancer across the population
- RSD based on a one-in-a-million extra risk (10^{-6} risk)
  - Probabilistic calculation incorporating uncertainty and variability
  - Traditional linear extrapolation: 10^{-5} / HED

Individual Risk Estimation

- HD_M^I: the human dose at which a fraction (or incidence) I of the population shows an effect of magnitude (or severity) M or greater for the adverse effect
  - I = 1%
  - M = 1×10^{-2}, 1×10^{-4}, 1×10^{-6}

Uncertainty Contribution Characterization

- Fraction of the overall variance that is contributed by uncertainties to quantify the D-R relationship
  - BMD model choice
  - BMD model parameters
  - Interspecies toxicokinetics and toxicodynamics
  - Intraspecies variability