

Cancer Dose-Response Data Collection and Cleansing

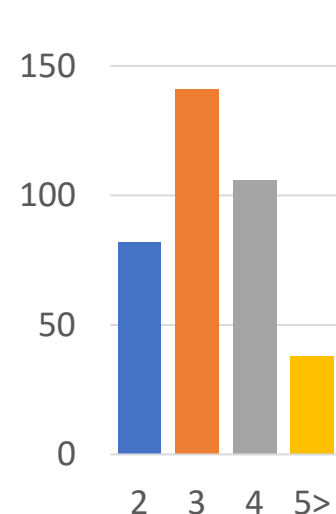
Data Collection

- 880 Toxicity values and study information – Wignall et al. (2014)
- 3,064 Toxicity values and study information – Masterfile (2017)

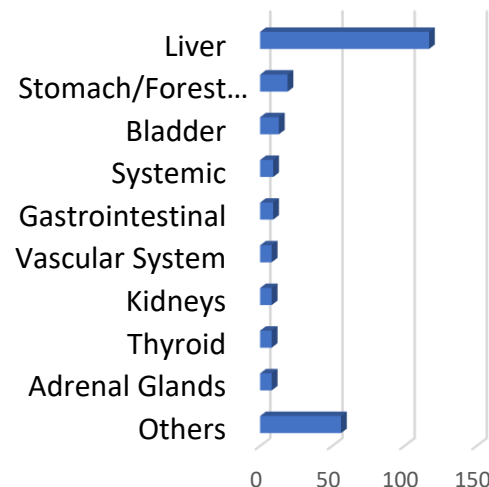
Data Cleansing - 255 Oral slope factors (OSFs)

- More than 3 dose-response data points
- No intraperitoneal administration

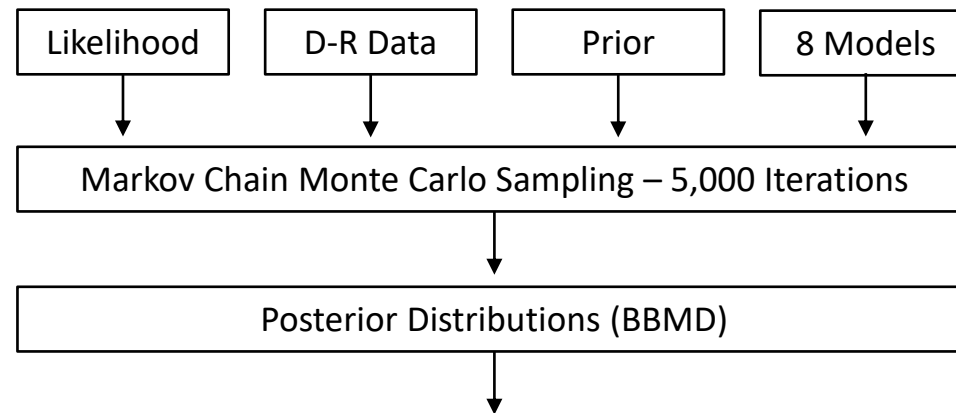
No. of D-R data points



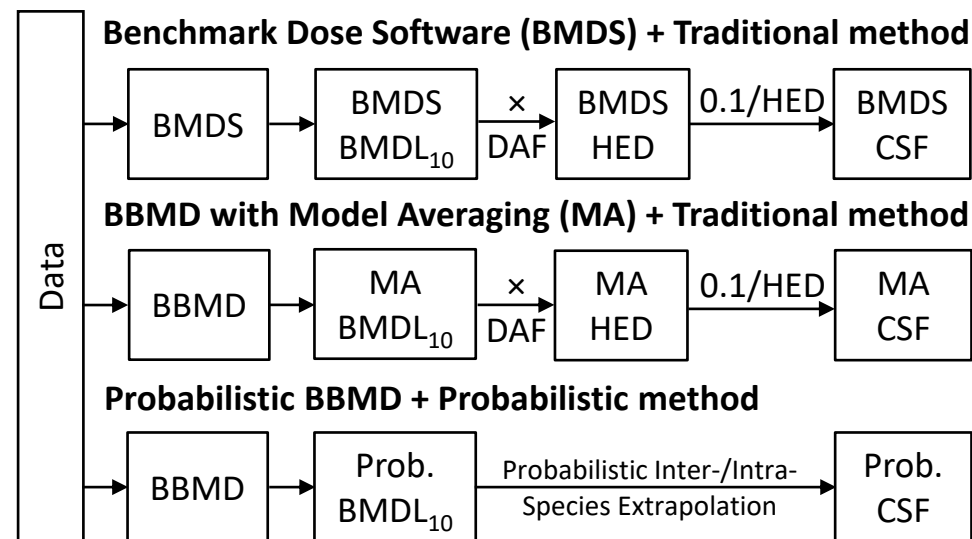
Cancer Organ Types



Bayesian Benchmark Dose (BBMD) Modeling and Probabilistic Extrapolations



Model Comparison to Traditional Approaches



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: 1×10^{-6} / CSF

Individual Risk Estimation

- Human Dose Associated with an Effect of Magnitude M and Population Incidence I (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
 - $I = 1\%$, $M = 1 \times 10^{-2}$, 1×10^{-4} , 1×10^{-6}

Uncertainty Contribution Characterization

- Fraction of the overall variance that is contributed by uncertainties to quantify the dose-response relationship
 - BMD
 - Interspecies toxicokinetics and toxicodynamics
 - Intraspecies variability