Preclinical toxicology data from the eTOX project (Sanz et al., Nature Reviews Drug Discovery, 16 (2017), 811–812) was analysed to provide background rates and treatment-related values on clinical pathology and histopathology datasets. Reference intervals and distributions for 20 of the most common clinical pathology parameters in rat and dog were generated, decision thresholds were applied to relabel data considered to be anomalous, and maximum fold change estimates calculated for each of these parameters. Background histopathology incidence rates in the liver, heart and kidney were also generated, with anomalous data relabelled using a Bayesian model to identify dose-dependent increases in pathologies. The outputs from this study include a mechanism for analysing newly generated data, rates and distributions that can be used to build predictive dose-response models, and a means to correlate treatment-related clinical pathology findings with concurrent histopathology findings.

Clinical pathology reference intervals

- Clinical pathology data was grouped by species, sex, and strain.
- For each group and parameter a mixture of "healthy" values, increased values and decreased values were observed.
- For each parameter a mixture model was developed that allows dose dependent trends to be calculated in the presence of a known background rate.
- Abnormal findings match expert calls from the eTOX database, with ROC-AUCs of 0.92 and 0.86 for increased and decreased calls respectively.

Histopathology background rates and anomalies

- Histopathology results were standardised in line with the eTOX histopathology and organ ontologies.
- A graph database was used to allow aggregation of the data over species, sex, pathology and organ.
- Background incidence rates were calculated from multiple studies control data and can include subtypes of the queried organ or pathology, e.g., "liver" can include results from "liver left lobe" and "liver right lobe".
- A Bayesian dose-response model was developed that allows dose dependent trends to be calculated in the presence of a known background rate.
- Abnormal findings, adverse effect levels and point-of-departures can be automatically identified by analysis of the findings, dose dependent trends, and background incidence rates.
- Abnormal findings show good agreement with expert treatment-related calls from the eTOX database (ROC-AUC = 0.84).