Reproducibility and Variance of Liver Effects in Subchronic and Chronic Repeat Dose Toxicity Studies

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In vivo studies provide reference data to evaluate alternative methods for predicting toxicity. However, the reproducibility and variance of effects observed across multiple in vivo studies is not well understood. The US EPA’s Toxicity Reference Database (ToxRefDB) and guideline studies include subchronic (SUB) and chronic (CHR) studies. The current work focused on the reproducibility of liver effects in SUB and CHR studies, as well as variance of weight, gross and histopathology are required by these guidelines. The objectives of this work include: (1) the variance in observed liver effects in SUB and CHR studies; (2) the probability that liver effects were observed in replicate CHR studies, as evaluation of liver weight, gross and micropathology are required by these guidelines. The current work focused on the reproducibility of liver effects in SUB and CHR studies, as evaluation of liver weight, gross and micropathology are required by these guidelines.

Methods

- **Data source**: US EPA’s Toxicity Reference Database (ToxRefDB) and guideline studies included subchronic (SUB) and chronic (CHR) studies.
- **Guideline or guideline-like studies from various sources**.
- **Variance Estimation**
  - **Concordance Analysis**
    - Compare prediction back to original data to see how well the model predicted observed results.
    - **Variance Estimation**
      - **Explained**
      - **Percentage**

Results

- **Variance Estimation**
  - **Anosim**
    - Evaluate the variance in observed liver effects in SUB and CHR studies.
    - **Conclusion**
      - **Variance**

Conclusions and Future Directions

- **Conclusions**
  - **Future Directions**
    - **Objective**
    - **Evaluation**
    - **Prediction**
    - **Conclusion**

For 2,4-Dichlorophenol, studies using male and female rats had overlapping dose ranges and all demonstrated observed liver effects. For Dichlorodiphenyltrichloroethane (DDT), studies using male and female rats had overlapping dose ranges and all demonstrated observed liver effects.

**Figure 2**: An example of 4 chemicals used in the liver test case. The dose range, study type, species tested, and absence or presence of liver effects for each study of a chemical.