Presentation Abstracts and Background Materials

SCIENTIFIC ADVISORY COMMITTEE ON ALTERNATIVE TOXICOLOGICAL METHODS

Session 3: Curating and Characterizing Data for Alternative Methods Use
Thursday, September 3, 2020

➢ Incorporating Variability in Animal Studies into Regulatory Frameworks and NAM Assessment

Presenter: **Dr. Nicole Kleinstreuer, NIEHS/NICEATM**

Establishing scientific confidence in New Approach Methodologies (NAMs) requires an in-depth understanding and characterization of the existing regulatory standard animal tests that they are targeted to replace. To this end, many recent ICCVAM and NICEATM efforts have been focused on curating and analyzing large datasets of legacy animal studies to understand the inherent variability in these reference endpoints and consequently set appropriate performance expectations for NAMs. This talk will provide a high-level overview of those efforts, ranging from studies targeting endocrine disruption (uterotrophic, Hershberger) to acute topical toxicities (skin sensitization, skin and eye irritation/corrosion) to acute oral systemic toxicity. Depending on the complexity of the study design and the measured endpoints, differing levels of variability are observed in the animal studies. Some of the observed variance is attributable to study design, but most of it appears to represent the inherent uncertainty in the animal as a model system. This is further confounded when considering the classification thresholds being applied to the data, as in the example of eye irritation where the reproducibility of the middle (mild/moderate) categories are essentially random based on replicate tests, and there is actually a higher probability that a chemical found to be a mild irritant in one test will not be classified in a repeat study. In some cases, such as skin sensitization, the sources of variance can be removed by applying stringent inclusion criteria, e.g. for vehicle, testing concentrations, curve fitting methods, etc. This was done via a multi-year process to develop a reference dataset for use in an OECD project, but is not reflective of the reality of regulatory submissions and animal study data that are often used to make risk assessment decisions.

Background

- Analysis of Draize Eye Irritation Testing and its Prediction by Mining Publicly Available 2008-2014 REACH Data
- Development of a Curated Hershberger Database
- Variability in the Rabbit Skin Irritation Assay (NICEATM poster presentation)

➢ Quantitative Variability in Repeat Dose Toxicity Studies: Implications for Scientific Confidence in New Approach Methodologies

Presenter: **Dr. Katie Paul-Friedman, Environmental Protection Agency/ODR**

NAMs for hazard are often evaluated or trained with animal studies; however, variability in animal study data limits NAM accuracy. The U.S. Environmental Protection Agency Toxicity Reference Database (ToxRefDB) enables consideration of variability in effect levels, including the lowest effect level (LEL) for a treatment-related effect and the lowest observable adverse effect level (LOAEL) defined by expert review, from subacute, subchronic, chronic, multi-generation reproductive, and developmental toxicity studies. The objectives of this work were to quantify the variance within systemic LEL and LOAEL values, defined as potency values for effects in adult or parental animals only, and to estimate the upper limit of NAM prediction accuracy. Results from this work suggest that the maximum amount of explained variance approach 55 to 73% for a NAM-based predictive model of systemic toxicity using these data as reference. The root mean square error

(RMSE) ranged from 0.47 to 0.63 log_{10}-mg/kg/day, depending on dataset and regression approach, suggesting that excellent NAMs that contribute little to no variability would predict a given systemic toxicity POD within approximately ± 1 log10-mg/kg/day of a reference or training value. These findings suggest data-driven considerations for building scientific confidence in NAM-based systemic toxicity predictions. Further, these findings can be applied in point-of-departure prediction using quantitative structure activity relationship models in order to report confidence intervals for these predictions that may be useful for informing chemical safety assessments. *This abstract des not necessarily reflect U.S. EPA policy.*

Background

- Variability in In Vivo Studies: Defining the Upper Limit of Performance for Predictions of Systemic Effect Levels

➢ Machine Learning in Toxicology: Towards Intelligent Access to the Content of Research

Presenter: **Dr. Robert Patton, Oak Ridge National Laboratory**

While machine learning and natural language processing research made incredible strides in many applications including facial recognition and sentiment classification, many domain-specific problems such as systematic review data extraction, scientific hypothesis generation, or even subject classification still represent manual and labor-intensive tasks. In this talk, I will present three areas where we are applying machine learning methods to increasingly automate aspects of the research workflow and reduce the time and human investment required to complete critical tasks.

Though early in the development process, we are leveraging deep learning principles developed for image recognition to extract structured information including sections, references, images, and tables from scientific documents. This approach enables us to overcome many limitations of existing tools and provide an accurate extraction method for many documents, which were previously not accessible by machine learning tools, such as scanned, purely image-based documents.

To support systematic review automation, we are developing tools to automate data extraction. Historically, developing accurate extraction models requires documents with detailed sentence- or word-level annotations. However, in many domains, such detailed annotations are not available and can be extremely expensive to create at the scale needed for state-of-the-art models to work well. We have developed an unsupervised approach that leverages pre-trained word embeddings to identify sentences and short text segments which likely contain target information and are leveraging transfer learning to increase the accuracy and scalability of this approach.

Finally, in our most recent work, we have applied a scalable graph algorithm on a knowledge graph created from research literature towards generating novel hypotheses from existing research. We have shown extracting information about the shortest path between two pairs of biomedical concepts has the potential to recommend novel relations for study before their discovery.

Background

- Unsupervised Identification of Study Descriptors in Toxicology Research: An Experimental Study
- DeepPDF: A Deep Learning Approach to Analyzing PDFs

➢ Machine Learning in Toxicology: Towards Intelligent Access to the Content of Research

Presenter: **Dr. Joseph Wu, Stanford University School of Medicine**

Heart disease is the most significant cause of morbidity and mortality in the industrialized world, accounting for nearly 25% of all deaths in the United States alone. While the use of human induced pluripotent stem cell (iPSCs) in

regenerative medicine is a long-term goal, a growing body of studies has shown promising results in the fields of drug discovery, development, and toxicity screening. Specifically, recent technological advancement has enabled the generation of patient-specific and disease-specific human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) in vitro. These iPSC-CMs carry all the genetic information from the individuals from whom they are derived. Here I will discuss recent advances in this technology and how it may be used for elucidating mechanisms of cardiovascular diseases, for drug testing, and for precision medicine.

Background

- Use of Human Induced Pluripotent Stem Cell-derived Cardiomyocytes to Assess Drug Cardiotoxicity
- Patient and Disease-specific Induced Pluripotent Stem Cells for Discovery of Personalized Cardiovascular Drugs and Therapeutics