Challenges & Opportunities: Establishing Scientific Confidence for Specific Fit-for-Purpose Use

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Our Previous Work

Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes. Patlewicz G, Simon TW, Rowlands JC, Budinsky RA, Becker RA. Regul Toxicol Pharmacol. 2015 Apr;71(3):463-77.

Developing scientific confidence in HTS-derived prediction models: lessons learned from an endocrine case study. Cox LA, Popken D, Marty MS, Rowlands JC, Patlewicz G, Goyak KO, Becker RA. Regul Toxicol Pharmacol. 2014 Aug;69(3):443-50.

Use and validation of HT/HC assays to support 21st century toxicity evaluations. Patlewicz G, Simon T, Goyak K, Phillips RD, Rowlands JC, Seidel SD, Becker RA. Regul Toxicol Pharmacol. 2013 Mar;65(2):259-68.

Scientific Confidence Framework

1. **Analytical Validation**
2. **Qualification**
3. **Utilization**

Scientific Confidence Framework

1. Analytical Validation

Assessment of the biological basis and analytical performance of assays.

- Each assay should map to a defined mechanistic endpoint (e.g., a key event in the mode of action or AOP).
- A defined chemical domain of applicability
- Documentation of assay performance characteristics (reliability, sensitivity, and specificity)
- Transparent data sets (to enable independent verification) should be readily available.

Note This framework was used to form the basis of the draft OECD guidance “Characterizing non-guideline in vitro test methods to facilitate their consideration in regulatory applications”

Scientific Confidence Framework

2. Qualification

Assessment of the prediction model derived from the assays.

- A defined algorithm for each prediction model.
- Appropriate measures of goodness-of-fit, robustness and predictivity of the prediction models (models may be quantitative or qualitative).
- Known limitations of each prediction model should be summarized.
- Prediction models should be characterized in sufficient detail to facilitate review, reconstruction and independent verification of results.

Scientific Confidence Framework for

3. Utilization

Contextual and weight-of-evidence analysis of the use (qualitative or quantitative) of the prediction model for a specific purpose.

- Defining the intended purpose of the prediction model
- Documenting/justifying applications, based on weight of evidence, the scientific confidence to support fit for purpose use of the prediction model(s).
    - (1) priority setting, where the model is used to identify priority substances that will go on to more detailed evaluation;
    - (2) screening level assessment
    - (3) read across to describe/predict a hazard property in lieu of a traditional tox study
    - (4) integrated testing strategy, or where the model is used in decision tree context
    - (5) to predict an adverse outcome.

Discussion is Needed by the Regulatory Science Community

How accurate must predictivity be for different decision contexts?

- *Articulate that different levels of confidence OK for different uses (e.g. priority setting vs. hazard ID*
- *Challenge how can these be described? in quantitative scientific terms?*

How can *integration of exposure with new alternative methods & prediction models (Rotroff et al., 2010; Becker et al., 2014, Wetmore et al. 2015, Shin et al 2015) provide an improved context for decision making?*

Rotroff et al. Toxicol Sci. 2015 Nov;148(1):121-36.
Becker et al Birth Defects Res B Dev Reprod Toxicol. 2014 Feb;101(1):114-24
Wetmore et al. Toxicol Sci. 2015 Nov;148(1):121-36
Shin et al. Environ Sci Technol. 2015 Jun 2;49(11):6760-71

Prediction Analytics Toolkit

Chemical safety evaluations continue to rapidly accelerate towards the replacement of traditional testing with prediction modeling for determining hazards and risks. Robust analytical tools for detecting, analyzing, quantifying, and visualizing associations and other relations (such as information relations among multiple variables) in data are critical for both development and evaluation of prediction models. The **Prediction Analytics Toolkit (PAT)**, an Excel add-in developed by Cox Associates with support from the American Chemistry Council, provides a point-and-click interface for doing advanced prediction analysis from Excel using R packages, even if the user does not know R. The PAT gives simplified access to the analytics power of a vast array of R packages for detecting, analyzing, quantifying, and visualizing associations and other relations (such as information relations among multiple variables) in data sets using standardized, well-documented, and well-supported algorithms. For users who have no knowledge of R, a few mouse clicks will display results from advanced R packages without the need to learn R.

Prediction Analytics Toolkit

- The PAT enables efficient development, cross-validation, and evaluation of the performance of predictive models from HTS (e.g. ToxCast) or other (QSAR, omics etc.) datasets.
- The PAT can help identify the specific characteristics of chemicals and responses for which predictive models work well (or poorly).
- The PAT can also identify subsets of predictors that are most (and least) important for predictive accuracy, including identifying any redundant or low-value-of-information assays that add little or nothing to predictive accuracy.

Thank You for Your Attention

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