CHANGES BASED ON NEW KNOWLEDGE?

YES THERE ARE MANY POSSIBLE CHANGES INCLUDING:

NEW SOURCES OF HUMAN CELLS,

AVAILABILITY OF COMPARATIVE CROSS STRAINS,

IMPROVED PREDICTIVE MODELS THAT CAN BE USED TO SUPPLEMENT AND EXPAND OUR KNOWLEDGE AND DOMAINS OF APPLICABILITY BY IMPROVING OUR ABILITY TO WORK ACROSS BIOLOGICAL LEVELS OF COMPLEXITY

WE CAN SIGNIFICANTLY ADD TO ALL LEVELS OF THE 3 RS

DISEASE BASED MODELS

- Disease based models are important tools not only for hazard identification but also for basic mechanistic research.
- However, please note that most environmental chemicals do not know nor were designed to be disease specific hence using only disease models for screening are useful but not sufficient for screening
- Biological endpoint screen can be useful if able to be placed within a systems basis for integration

IS READ ACROSS A VALUABLE APPROACH FOR CHEMICAL HAZARD AND RISK ASSESSMENT

- Any information is potentially useful however it depends on what question you are asking?
- The similarity of the context for which the read across operation is being used and the types of information that you will use for your read across is critical to being able to accurately answer this question. QSAR is an example of where some basic information can be extremely useful in screening but is usually not sufficient without addressing large areas of uncertainty with some types of extrapolation. (look at remaining challenges for substitutions)

CAN WE ADD ENDPOINTS THAT ARE USEFUL FOR MOA?

- Of course, knowing dose response information for a variety of potential critical pathways is important and some examples of this have been demonstrated with the Computational Tox databases.
- For example, bioassay data can be useful for determining some very basic responses in vitro and for looking at receptor binding and response relationships.
- However ensuring that the domain of coverage is adequate across endpoints is important. Do we feel as if we are complete for endpoints such as immune response and change? Neurofunctional?, etc.
- More quantitative endpoints that link responses at lower levels would be important to capture toxicodynamics.

USE OF PHARMACOKINETIC DATA

- Of course and also linked toxicokinetic and dynamic models are needed
- Need to look at the Expo cast models and the variability seen in exposomic studies. Good example are the PFAS, why were we so far off from actual exposures. This was more than pharmacokinetics at play in these examples.