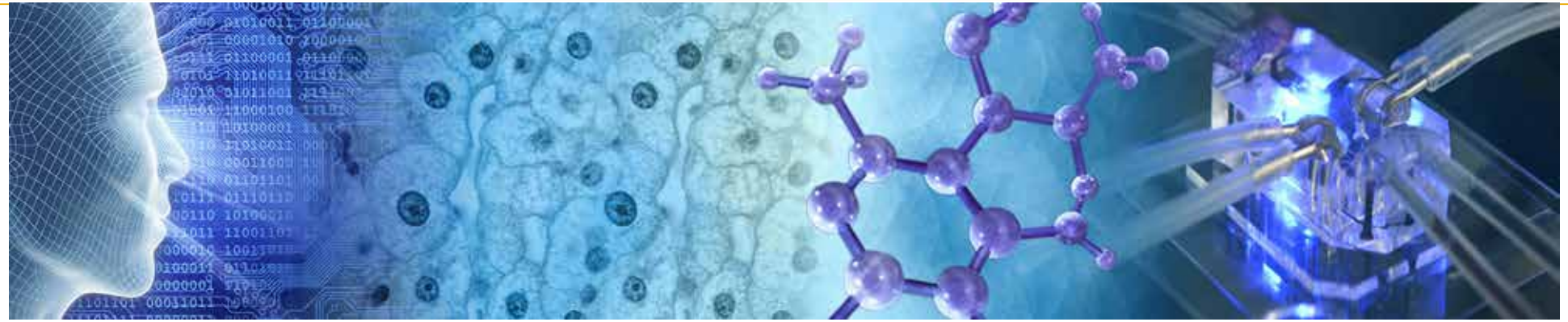
NTP
National Toxicology Program



Operationalizing findings and recommendations

October 30-31, 2019

Mixtures

- What types of mixtures?
  - Medical devices, cleaning products, mixtures of industrial chemicals, “tank” mixtures; agchem, others?
- Additivity
  - Datasets are skewed towards nontoxic
  - Critical to be transparent about applicability (does it break down where dose response info is needed?)
  - Mechanistic interactions not taken into account; also no ADME
  - Confidentiality of formulations remains a challenge – pharma example: IQ Consortium
    - Must address this to successfully build models for mixtures (or to optimize additivity)

Leveraging Artificial Intellegence

- NOTE: need to make sure that the variability dataset is annotated to indicate what protocol, etc. where possible; this is important to best characterize variability of the assay based on a consistent protocol
- Ultimately regulators want to know how large of a confidence interval for the model prediction is OK (or, how far from an available LD50 is OK for the model prediction?)
- Transparency is essential
- Need to develop a threshold of concordance that indicates the prediction is high confidence
- Need to evaluate where the data come from as a variable when looking at model performance
  - i.e., need to be sure that results aren't by chance ("it's right for the right reasons") so that regulators can defend/describe results; NOTE – 5th OECD principle: mechanistic interpretation

Information Gaps

- Where current models are successful in predicting LD50 classes:
  - Reactives, denaturants, hydrocarbons, chelants, aconitase inhibitors, anticoagulants
- Classes of chemicals/mechanisms for which specific assay/model development is needed to predict acute toxicity:
  - Nervous system, adrenergic compounds, cardiac channel actives, for example
  - Metabolism to cyanide, H_2S, aconitase, phosphothionates, for example
- Mechanistic read across can be used to fill data gaps
  - Need to be careful with metabolic matters & *in vitro.*
- Limitations of computational models and how can biological information complement their utility:
  - Computational models often use read-across without understanding MOA
  - Statistical models biased towards non-toxic compounds yet the highly toxic compounds are ones need to ensure we can identify
  - *In vitro* models should address specific mechanisms, sub-mechanisms and metabolism

Information Gaps

- Misclassification of chemicals by existing in vitro/in silico methods could be due to:
  - Unequal GHS distribution; need to tie MOAs to in vitro models; metabolism; cytotoxicity assays vary; detoxification; reactive chemistries reacting with water, etc
- Mechanisms of acute lethality are needed for MOAs that drive high acute toxicity
- Mechanistic assays work best for:
  - Receptor binding assays w/o metabolism
  - Validated screens skin sens, eye/skin irritation
- When are we concerned with mechanism in making a risk assessment decision? When are we not, i.e. when can risk assessment decisions be made simply based on LD50/classification without mechanistic information?
  - When models predict very high acute toxicity and willing to classify
- Chemical and/or biological clustering can inform testing strategies and regulatory decisions
  - Eg., clustering by mechanism for mechanistic read-across

Action Items

- Variability analysis – need it to establish confidence
  - Ideally focus the analysis on guideline-like studies (or in comparison to an overall analysis)
- Additivity – EPA-OPP pilot + existing publications
  - Can we identify non-toxics without in vivo testing?
- Explore adding biological/mechanistic information to complement in silico predictions
  - Critical to include metabolism
  - Systematically catalog the mechanisms of acute toxicity and available associated assays; match these mechanisms to chemicals
- Consider AOPs to identify available information (and where information gaps exist)
  - NOTE: can be very simple and don’t require lengthy
- **Critical to it all: transparency and training**

Acute Mechanisms – Data Gaps

High acute tox

Voltage-gated channels (Na^+, K^+, Ca^{++})	Dopaminergics
Protein synthesis inhibitors	Histaminergics
Dihydrofolate reductase inhibitors	Endoplasmic reticulum Ca^{++} channels
TRPA1	NMDA receptor inhibitors
Adrenergics	Cardiac channel blockers
Opioid receptor	Remaining AhR scaffolds
Tubulin binders	Heme biosynthesis inhibitors
Norepinephrine reuptake inhibitors	Serotonin reuptake inhibitors