Development of a Rapid Risk Assessment Process and Software Tools to Support Air Force Operational Decision-making and Technology Acquisitions

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Presentation to SACATM
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Rapid assessment of chemical risk

-6.2 effort to develop comprehensive model to predict individual susceptibility to chemical risk
Main Goal: Rapid assessment of human health risk due to operational chemical and physical stressors

Key Deliverable(s)/Product(s):

- **In silico models**: Curated collection of prediction models for human toxicity
  - Focused on rapid assessment of new or novel chemistries, incorporating knowledge of AF relevant exposure scenarios and physiological stressors

- **In vitro data**: Collect necessary data to improve prediction of AF chemical risk
  - Expand chemical domain of current models to improve in silico predictions for AF-specific exposures

- **Risk assessment workflows**: Curated workflow to streamline assessments
  - Initial focus is on neurotoxicity and inhaled hazards
Predictive risk products
- 6.3 products to support rapid risk assessment & chemical decisions

ToxAdvisor-lite
(Mobile app)
- Exposure guidelines
- Risk predictions
- Recommend next steps

ToxAdvisor
(Desktop application)
- Exposure guidelines
- Curated risk predictions and models
- Risk calculations, workflows

Predictive Risk Capability Build
- Exposure guideline database
- Risk prediction models
- Toxicity data database
- Dosimetry models
- Exposure scenario catalog
- Risk assessment workflows

Customer-facing

User POV - assessment process

App content process
Rapid Risk Assessment Workflow

1. **Qualitative** (i.e., hazard identification)
   - Known target toxicity?
   - Available OpEL?
   - Sufficient results?

2. **Mechanistic data?**
   - Conduct in vitro tests
   - Conduct read-across
   - Sufficient results?

3. **Chemical structure?**
   - Conduct QSAR/AI modeling
   - Sufficient results?
   - Dosimetry models (PBPK, MPPD)
   - Re-visit problem formulation

4. **Sufficient information for risk assessment?**
   - Exposure > uncertainty factor ÷ OpEL?

5. **Novel chemical**
   - Conduct in vivo extrapolation (iVIVE)

6. **Higher risk**
   - Lower risk
**Rapid Risk Assessment Workflow**

1. **Known target toxicity?**
   - **Mechanistic data?**
     - **Available OpEL?**
       - **Acute toxicity data?**
         - **Sufficient information for risk assessment?**
           - **Exposure > uncertainty factor ÷ OpEL?**
             - **Higher risk**
             - **Lower risk**

2. **Chemical structure?**
   - **Conduct read-across**
     - **Sufficient results?**
       - **Conduct QSAR/AI modeling**
         - **Sufficient results?**
           - **Conduct in vitro tests**
             - **Conduct in vivo extrapolation (IVIVE)**
               - **Dosimetry models (PBPK, MPPD)**
                 - **Re-visit problem formulation**

3. **OpEL?**
   - **Known target toxicity?**
     - **Quantitative (i.e., risk level)**
   - **Qualitative (i.e., hazard identification)**
Rapid Risk Assessment Workflow

1. **Qualitative (i.e., hazard identification)**
   - Known target toxicity?
   - Mechanistic data?
   - Available OpEL?
   - Acute toxicity data?

2. **Quantitative (i.e., risk level)**
   - Conduct in vivo extrapolation (IVIVE)
   - Sufficient results?
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3. **Sufficient information for risk assessment?**
   - Chemical structure?
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4. **Exposure > uncertainty factor ÷ OpEL?**
   - Higher risk
   - Lower risk

5. **Novel chemical**
   - Conduct in vitro tests
   - Conduct QSAR/AI modeling
   - Sufficient results?
Current research efforts

1. TRV database & decision process
2. OpEL generation
3. Acute toxicity data/models
4. Read-across – preliminary OpEL
5. Acute toxicity QSAR model
6. Neurotox AI model
7. Mitochondria QSAR model
8. Lung toxicity QSAR model
9. Lung toxicity in vitro: surfactant (collaboration with Dr. Hussein)
11. Neurotoxicity in vitro: LTP/biomarkers (SBP)

- Conduct in vivo extrapolation (IVIVE)
- Conduct in vitro tests
- Conduct read-across
- Conduct QSAR/AI modeling
- Conduct in vitro tests
- Dosimetry models (PBPK, MPPD)
- Rapid PBPK model process

- Sufficient OpEL?
- Available OpEL?
- Known target toxicity?
- Mechanistic data?
- Chemical structure?
- Sufficient results?
- Frieden's energy of a chemical change
- Chemical structure
- Available data

- Re-visit problem formulation
- Higher risk
- Lower risk
- Exposure > uncertainty factor / OpEL?
QSAR models: Predicting Acute Toxicity of Poorly Characterized Chemicals

- Novel AI model
- Predicts toxic/nontoxic based on GHS classification, chemical structure

Message passing neural network (MPNN) model

Built on >40,000 chemical database

Used to predict toxicity of > 250,000 chemicals

Model validation

ACC = (TP+TN)/Nchem – accuracy
AUC – area under ROC curve
Artificial Intelligence models: Neurotoxicity Target Prediction

- Novel AI model
- Predicts ligand binding to neurotransmitter receptors

Neuro targets
- Acetylcholine
- AChE
- AMPA
- CHAT
- GABA
- Glutamate
- Glycine
- DRD2,3&4
- Kinate
- PX2
- Serotonin


McCarthy et al. 2022.
Rapid risk assessment products: creating databases, workflows and prediction tools for toxicity reference values

Hazard quotient (HQ) = Measured air concentration / toxicity reference value
Hazard index (HI) = sum of HQs for all chemicals

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<th>Tier 1 Minimum Ceiling equiv. TRV (C, IDLH, STEL) (ppm)</th>
<th>Tier 2 Minimum OEL (8-hr TWA) (ppm)</th>
<th>Tier 2 Minimum Acute TRV (10-min to 1 hr) (ppm)</th>
<th>Tier 2 Minimum C equiv. TRV (CRIT, up to 1 hr) (ppm)</th>
<th>Tier 2 Minimum TRV (14-dy to 1 yr) (ppm)</th>
<th>Tier 3 Minimum OEL (8-hr TWA) (ppm)</th>
<th>Calculated Ceiling Equiv. (lowest occup TWA*3)</th>
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Estimate preliminary TRV from nearest neighbor, using ICE tanimoto score tool
Inhalation toxicity – predicting toxicity for poorly characterized chemicals

Surfactant effects
Irritation/Corrosion
Interaction with cell membrane
Physical injury

Clippinger 2016 – NICEATM webinar
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Possible homepage includes:

- Risk overview – allows 1-click results for OpEL/Hazard
- Guided assessment provides user assistance in decision-making
- More detailed information if desired
- User guidance
  - Provide context, recommendations for next steps
Inhalation Hazard

Chemical Hazards
- Inhalation
- Dermal
- Oral
- Eye Irritation
- Skin Sensitization
- Skin Irritation

Operational Exposure Limits (OpEL)

Do Not Exceed
- 6-15 Min Max: 56,186 ppm
- 1 Hour: 0.896 ppm
- 14 Day: 0.016 ppm

Potential Health Risk

Exposure Danger
- Eye Damage: Category 2A
- Skin Irritation: Category 4B
Mobile App – **Output and utility**

**Results provide data & context:**

- Requested endpoint actual value vs. predicted
  - If only predicted is available, user alert will call attention to the fact this is a predicted value

- Graphic provides context:
  - Comparison to well known “benchmark chemicals”
  - Rank order to show relationship to benchmark chemicals and greater chemical database
  - Color coding indicates relative toxicity classification

- Automated professional judgement
## Current Activities

### Database

**Toxic Effect**
- **GHS labels**
- **In vivo data**
  - EPA, NIH/NTP/NICEATM
  - ECHA/REACH, DoD/DTIC
- **In vitro data**
  - HT assays (ToxCast, OECD)
  - Organotypic assays (DoD, published, collabs)
  - Cardiac, lung*, CNS*

### Predictive Models
- 6-pack acute toxicity model*
- QSAR-based structural alerts*
  - Acute toxicity
  - Allergic contact dermatitis*
  - Skin/eye corrosion, etc.
- Read-across
- Machine learning models*
  - Neurotoxicity*
  - Lung toxicity*

### Risk Level
- **Toxicity Reference Values**
  - AEGLS, MEGs, TLVs, etc
  - GHS classifications (1-5)
- **In vivo NOELs/LD50s**
- **In vitro NOELs/EC50s**

### Risk Assessment
- TTC categories (1-3)
- Read-across
- Systems biology models*

### Exposures
- **Historical data**
  - Common AF scenarios

### Dosimetry
- **Chemical properties**
- **Particulate characterization**

### Other exposure models
- JH/APL OE model*
- HTTK, rapid PBPK models*
- Chemical-specific PBPK*
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- Elaine Merrill
QUESTIONS?