Application of CATMoS to Ecological Risk Assessment

Kamel Mansouri
Computational Chemist
NIH/NIEHS/DNTP/NICEATM, RTP, NC, USA

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of US EPA or any federal agency.
Motivations

- **Organic pollutants** with exposure potential may accumulate in body tissues
  - Cause **toxic effects** to wildlife and humans
- **Several toxicological endpoints**
  - Important to **risk assessment** of chemicals
- Existence of **gaps in the experimental data** for environmental endpoints
  - Need to fill the data gaps and bridge the **lack of knowledge**
- **Regulatory requirements**:
  - Reduce **animal testing, time and costs**

\[
\text{(Q)SAR} = f(\text{mol})
\]

(Quantitative) Structure-Activity Relationship

**IN SILICO**
Collaborative projects

**CERAPP**
Collaborative Estrogen Receptor Activity Prediction Project (2015/16)
Mansouri et al. ([https://doi.org/10.1289/ehp.1510267](https://doi.org/10.1289/ehp.1510267))

**CoMPARA**
Collaborative Modeling Project for Androgen Receptor Activity (2017/18)
Mansouri et al. ([https://doi.org/10.1289/EHP5580](https://doi.org/10.1289/EHP5580))

**CATMoS**
Collaborative Acute Toxicity Modeling Suite (2017/18)
Kleinstreuer et al. ([https://doi.org/10.1016/j.comtox.2018.08.002](https://doi.org/10.1016/j.comtox.2018.08.002))
Mansouri et al. ([https://doi.org/10.1289/EHP8495](https://doi.org/10.1289/EHP8495))

Endocrine Disruptor Screening Program

Acute Toxicity Workgroup: alternative methods

ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods
Over 100 scientists from around the globe representing academia, industry, and government contributed.

Interactive map: https://batchgeo.com/map/9d3ff810a72d8a84093c74ab0601f01d
Acute Oral Toxicity: CATMoS

- ICCVAM is developing alternative test methods for the EPA’s six pack tests: Acute oral, dermal, inhalation, eye & skin irritation and skin sensitization

- Acute Toxicity Workgroup: identifies federal agency requirements, needs, and decision contexts for using acute systemic toxicity data
Agency-Based Modeling Endpoint Selection

**Binary Models**

- Highly toxic (≤50 mg/kg)
- Toxic (>50-5000 mg/kg)
- + Nontoxic (>2000 mg/kg)

**Continuous Model**

- Point estimates of LD50 values

**Categorical Models**

**EPA Categories**
- I (≤ 50 mg/kg)
- II (>50 ≤ 500 mg/kg)
- III (>500 ≤ 5000 mg/kg)
- IV (>5000 mg/kg)

**GHS Categories**
- I (≤ 5 mg/kg)
- II (>5 ≤ 50 mg/kg)
- III (>50 ≤ 300 mg/kg)
- IV (>300 ≤ 2000 mg/kg)
- NC (> 2000 mg/kg)

**Packing Group**
Coverage and concordance of the models

Consortium Comprised 35 Participants/Groups

- Very Toxic: 32 models
- Non-toxic: 33 models
- EPA categories: 26 models
- GHS categories: 23 models
- LD50: 25 models

Total: 139 models
Steps of combining the single models into consensus

**Initial models & predictions**
- VT (32 models)
- NT (33 models)
- GHS (23 models)
- EPA (26 models)
- LD50 (25 models)

**Combining models**

**Step 1**
- Weighted average/majority rule

**Independent consensus models/predictions**

- VT
- NT
- GHS
- EPA
- LD50

**Weight of Evidence approach (WoE)**

**Step 2**
- Majority rule

**Consistent consensus models/predictions**

- VT
- NT
- GHS
- EPA
- LD50

A consensus model per endpoint (~20--30 models)

Consensus representing all ~140 models

Learn more:
- https://youtu.be/KjbTnfRTY-0
## Performance Assessment

### Consensus Model Statistics

<table>
<thead>
<tr>
<th></th>
<th>Very Toxic</th>
<th></th>
<th>Non-Toxic</th>
<th></th>
<th>EPA</th>
<th></th>
<th>GHS</th>
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<td>Eval</td>
<td>Train</td>
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<td>Eval</td>
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<tr>
<td>Sensitivity</td>
<td>0.87</td>
<td>0.70</td>
<td>0.88</td>
<td>0.67</td>
<td>0.81</td>
<td>0.62</td>
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<tr>
<td>Specificity</td>
<td>0.99</td>
<td>0.97</td>
<td>0.97</td>
<td>0.90</td>
<td>0.92</td>
<td>0.86</td>
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<td>Balanced Accuracy</td>
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<td>0.84</td>
<td>0.92</td>
<td>0.78</td>
<td>0.87</td>
<td>0.74</td>
<td>0.88</td>
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<tr>
<td><em>In vivo</em></td>
<td>0.81</td>
<td></td>
<td>0.89</td>
<td></td>
<td>0.82</td>
<td></td>
<td>0.79</td>
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</table>

The consensus predictions perform just as well as replicate *in vivo* data do at predicting oral acute toxicity outcome.
Running CATMoS Consensus and other OPERA models

**OPERA standalone application:**
- Free, opensource & open-data
- Command line & Graphical user interface
- Single chemical and batch mode
- Multiple platforms (Windows and Linux)
- Embeddable libraries (java, C, C++, Python)
- **New: QSAR-ready standardization**

**OPERA models:**
- Physicochemical properties
- Environmental fate
- ADME properties
- Toxicity endpoints

**Input options:**
- Structure IDs (CAS, DTXSID, InChIKey)
- Structure files (SMILES, SDF, Mol)

**Links:**
- [https://github.com/NIEHS/OPERA](https://github.com/NIEHS/OPERA)
- [https://ntp.niehs.nih.gov/go/opera](https://ntp.niehs.nih.gov/go/opera)
- [https://doi.org/10.1186/s13321-018-0263-1](https://doi.org/10.1186/s13321-018-0263-1)
Predictions on NTP/ICE

https://ice.ntp.niehs.nih.gov/Search
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<th>3</th>
<th>4</th>
<th>5</th>
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<td>3</td>
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<td>1</td>
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<td>2.26</td>
<td>[3-4.5]</td>
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- Consensus predictions for the 5 endpoints
- LD50 confidence interval (based on in vivo data variability)
- Applicability domain assessment
- Experimental values, when available
- Nearest neighbors, optional
Collaboration with ATWG partners and ICCVAM agencies

<table>
<thead>
<tr>
<th>Agency</th>
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<th>Agency</th>
<th>No. Substances</th>
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Progress made with EPA EFED and Humane Society of the US:

- Compared mammalian acute toxicity risks based on CATMoS predictions to those based on rat LD50 tests for 178 pesticides registered in the last 25 years.
- Determined overlap and discordance leading to additional curation of the data and prediction assessments.
The dataset: collection and curation

Initial steps:

• Initial list of 195 pesticides registered from 1998 to 2020
• Rodenticides and soil fumigants were removed
• Entries with conflicting or inadequate information were removed
• Certain entries adjusted or corrected based on alternate resources.

Curated dataset:

• Final list included 178 conventional pesticides
• 57 with LD50 point estimate values. Range: 62 mg/kg to >7500 mg/kg
• 121 with limit test LD50. 42 estimated at >2000 mg/kg and 79 at >5000 mg/kg
• 140 pesticides with publicly-available ecological RAs

<table>
<thead>
<tr>
<th>EPA category</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tbody>
<tr>
<td>Pesticides</td>
<td>0</td>
<td>12</td>
<td>84</td>
<td>82</td>
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</tbody>
</table>
The evaluation and analysis

The approach:

• Quantitative: Comparing risk quotients (RQs) based on predicted and empirical rat LD50s as available in the RAs (N = 100)

• Semi-quantitative: comparison made on worst-case scenario (N = 12)

• Qualitative: pesticides with no RAs or RQs calculated (N = 66)

The analysis steps:

• Evaluate concordance of empirical LD50s values used in the ecological RAs Vs the input data used for developing CATMoS

• Identify the CATMoS predictions that would and would not have affected the acute mammalian toxicity RA of the analyzed pesticides

• Characterize the model’s success in predicting risk in all or some of the exposure scenarios

• In discordant cases, identify whether the model tends to be more or less conservative than the available RAs.

• Use the quantified margin of uncertainty around in vivo LD50s to estimate the overlap between predictions and empirical values
Next steps and goals

• Evaluate the applicability of CATMoS estimates as a potential replacement of the rat acute single oral dose study for establishing the effects endpoint in ecological risk assessments of conventional pesticides

• Iterative evaluation process to determine how and under what scenarios CATMoS may or may not be able to inform any future data needs for in vivo studies
The “3C” Concept at Work!

- Success of the projects was due in great part to the use of the 3C concept as well as up-front and continuous engagement of regulators in the process.

https://ntp.niehs.nih.gov/go/natl-strategy
Thank you for your attention!

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