An Open-source, Generalized Workflow for IVIVE Analysis

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Introduction

A critical challenge for implementing non-animal approaches for chemical safety testing is linking in vitro assay results to potential in vivo effects. A critical challenge for implementing non-animal approaches for chemical safety testing is linking in vitro assay results to potential in vivo effects. 

To facilitate IVIVE, we developed an open-source IVIVE tool that incorporates:

- In vitro assay data
- Quantitative structure-activity relationship (QSAR) models
- Reverse dosimetry using either one-compartment pharmacokinetic (PK) or multi-compartment physiological-based (PBPK) models

The IVIVE tool is openly available through the U.S. National Institute of Environmental Health Sciences (NIEHS) supported this poster. Technical support was provided by 1, W Casey; 3, N Kleinstreuer.

Figure 1. Predicting In Vivo EAD from In Vitro Activity Concentration

Figure 2. ICE and IVIVE Tool Overview

Figure 3. Screenshot of OPERA GUI

Figure 4. Structures of Models Used in IVIVE Tool

Figure 5. ICE IVIVE Tool Input

Figure 6. ICE IVIVE Tool Output

Figure 7. IVIVE Results Using PBPK Model for BPA

The PK Models Used in IVIVE

- The population-based PK model (Figure 4A) is a one-compartment model that:
  - Assumptions: 100% absorption,
  - Describes total clearance as the sum of hepatic and renal clearance
  - The model estimates steady-state plasma concentration (Css) following a given dose for a Monte Carlo simulated population that accounts for inter-individual variability, covering common demographics such as weight (Klimek et al. 2013)
  - The user has two options for calculating the EADs that would lead to aCss equivalent to the ACC: AACC; estimated in vitro activity of interest
  - EAD corresponding to unbound chemical concentration (default option)
    \[
    \text{EAD} = \frac{\text{ACC}}{\text{EAD}_{\text{ACC}}} \cdot \text{mg/kg/day} = \frac{\text{CSS}}{\text{EAD}_{\text{CSS}}} \cdot \text{mg/kg/day}
    \]
  - EAD corresponding to total chemical concentration:
    \[
    \text{EAD} = \text{ACC} \cdot \text{CSS} \cdot \text{EAD}_{\text{CSS}} \cdot \text{mg/kg/day}
    \]

- The PBPK model (Figure 4B) includes four compartments: gastrointestinal tract, liver, kidney, and remaining tissues (e.g., rest of body)
  - The model includes intestinal glucuronidation to simulate specifically' chemicals known to undergo intestinal glucuronidation (e.g., estradiol)
  - This model can calculate EADs corresponding to maximum plasma concentration (Css) corresponding to in vitro activity concentration.

Table 1. Comparison of IVIVE-PK Workflow Output with In Vivo Data

<table>
<thead>
<tr>
<th>Chemical</th>
<th>PK Workflow Output</th>
<th>In Vivo Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone</td>
<td>0.024</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>0.078</td>
<td>0.00025</td>
</tr>
<tr>
<td>17beta-Estradiol</td>
<td>0.017</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Discussion and Conclusion

- This workflow provides an open-source, easy-to-use tool for IVIVE. The tool can be used to evaluate the correlation between in vitro and in vivo activity for toxicologically relevant chemicals.
- For chemicals lacking in vivo data, the tool can be used to predict relevant toxicity potentials respecting the safety assessment process.
- When evaluating estrogenic activity, the range of EAD estimates produced by the test was considerably wide due to range of in vitro assay EDA results.

The IVIVE workflow using a multi-compartment PBPK model incorporating glucuronidation improved prediction accuracy for BPA and likely for other SRD-like chemicals.

References


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