Strategies to Integrate Exposure, PBPK Models and Data on Metabolism to Predict Plasma Levels of Compounds and their Metabolites that are Directly Comparable to *In Vitro* Toxicology Results

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On behalf of
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Measurement of dose in toxicology is now divided.
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Internal Concentration µM

Future

Admin. Dose mg/kg/d

Traditional
Measurement of dose in toxicology is now divided

<table>
<thead>
<tr>
<th>Internal Concentration µM</th>
<th>Admin. Dose mg/kg/d</th>
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</thead>
<tbody>
<tr>
<td>Future</td>
<td>Traditional Animal-based tox</td>
</tr>
<tr>
<td>In-vitro based tox</td>
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</tbody>
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Measurement of dose in toxicology is now divided

**Internal Concentration**

μM

Future

In-vitro based tox

Relevant to biomonitoring

**Admin. Dose**

mg/kg/d

Traditional

Animal-based tox

Linked to traditional exposure and risk assessments
Measurement of dose in toxicology is now divided into two categories:

- **Admin. Dose**
  - mg/kg/d
  - Traditional
  - Animal-based tox
  - Linked to traditional exposure and risk assessments
  - Avoids dealing with ADME

- **Internal Concentration**
  - µM
  - Future
  - In-vitro based tox
  - Relevant to biomonitoring
  - Integrates doses from multiple routes and time-varying exposures
Our current approach for connecting the two dose metrics (reverse dosimetry) can only predict the relationship under restricted circumstances (steady state conditions) and for limited numbers of chemicals.
Goals of Project

• Goal 1:
  – Tiered high throughput tools
  – Predict the time course of blood concentrations

• Goal 2: Metabolism in HTS risk assessments
  – Which chemicals
  – Assays
• Government, academia, and industry recognize the need to better connect internal and administered doses.
• Publications.
• RISK21 IVIVE subgroup.
• Structure-based predictions of metabolism and parameters required by PK and PBPK models are becoming more available.
Benefits

• Improved HTS risk assessments
  – More effective screening out low concern uses of specific chemicals
  – Ability to identify chemical-specific critical data for performing higher-tiered assessments

• Coordinate and establish best practices for the various groups working in this area.
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