ECHA Workshop: Accelerating the Pace of Chemical Risk Assessment

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NTP Board of Scientific Counselors
December 8, 2017
- A*STAR (Singapore)
- US Consumer Product Safety Commission
- California EPA
- US Environmental Protection Agency (EPA)*
- European Chemical Agency (ECHA)*
- European Food Safety Agency
- National Industrial Chemicals Notification and Assessment Scheme (NICNAS [Australia])
- National Institute for the Industrial Environment and Risks (INERIS [France])
- Joint Research Council (EU)
- Health Canada
- Safety and Health Technology Center (SAHTECH [Taiwan])
- National Institute for Public Health and the Environment (RIVM [Netherlands])
- Japanese Ministry of Health, Welfare and the Environment
- Korea Ministry of the Environment
- US National Toxicology Program
- Organisation for Economic Co-operation and Development (OECD)
• Why- Immediate drivers
  – TSCA reform act
  – REACH experience
  – Purpose
    • To “make the science of new approach methodologies (NAMS) work for common regulatory challenges”
    • “To bring together international regulators to discuss progress and barriers in applying new tools to prioritization, screening, and quantitative risk assessment of differing levels of complexity.”

• When and how-
  – Workshops to develop case studies
    • September 14-15, 2016 EPA Washington, DC
    • October 10-11, 2017 ECHA Helsinki, Finland
    • Periodic teleconferences
September 2016

- Using NAMS to address data poor, high exposure chemicals (ECHA)
- Use NAMS to improve chemical categories and biological activity groupings (EPA)
- In vitro bioactivity as a conservative PoD (EPA)
- New tools to predict exposures from various chemical structure and use categories (EPA)
- Develop multimedia exposure models to improve Pb mitigation efforts (EPA)
- Develop a range of validated NAMS to identify endocrine disruptors (France)
- Application of NAMS to perfluoroalkylated substances (EPA)
- Amphibian skin absorption models (EFSA)
- Develop reference doses from endocrine disruptors from in vitro assays (Korea)
- Medaka extended one generation reproduction assay (Japan)
Initial proposed case studies

**September 2016**

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• The PoD for changes in hepatic gene expression is predictive of the PoD for biological effects in any organ in any length study.
• Administer chemical to male SD rats by oral gavage once per day for 4-5 days at 6 to 8 levels covering a wide dose range, from MTD downward to predicted NOEL

• Remove liver on day 5-6 for transcriptomic assessment- microarray or RNA seq with S1500+ gene set

• Load gene expression files and process according to preset criteria through BMDExpress2.0

• Perform benchmark dose modeling for both gene level and “pathway” level hepatic transcriptome changes

• Compare BMDs for gene or pathway expression changes with BMDs for any traditional toxicological response
• Plots either active genes or “pathways” in an ascending accumulative manner based on increasing median BMD or BMD$_L$

• Provides view of most to least dose sensitive gene or pathway

• Can identify genes or pathways by mouse click
**p-Toluidine, N,N-dimethyl-p-toluidine 5-day genomics study**

- **N,N-dimethyl-p-toluidine (DNPT)**
  - Hepatocellular tumors and liver toxicity in rats and mice
  - Nasal transitional epithelial adenoma/carcinoma and nasal toxicity in rats
- **p-Toluidine (p-Tol)**
  - Hepatocellular tumors in mice and liver toxicity in rats and mice
- **Methemoglobinemia**
  - Both chemicals through a postulated p-methyl phenyl hydroxylamine
- **Compare transcriptomic profiles**
DMPT and \( p \)-toluidine 5-day genomics study design

- **Model**: F344/N Rat (male)
- **Route**: Oral (corn oil gavage)
- **Dosing regiment**: 5 repeated doses, euthanize 24 hrs after last dose
- **Dose groups**: 6
  - 0, 1, 6, 20, 60, 120 mg/kg/day
- **Group size**: 5
- **Organ for transcriptomics**: Liver
- **Other endpoints**: Clinical observations, body and organ weights, clinical pathology
“Active” GO BP Terms

Genes

DMPT GO BP and gene BMD values

2 Year/LOAEL (Liver/nose)
5 Day NOEL (liver)

2 Year LOAEL (Liver/nose)
5 Day NOEL (liver)
“Active” GO BP Terms

DMPT 2 Year/LOAEL (Liver/nose)
5 Day NOEL (liver)

Genes
• What kinds of substances do we miss? Why?
• Do kinetic adjustments adequately accommodate bio-accumulative substances?
• Non toxic substances will produce gene expression changes- Do we care?
• Can this approach be used for more than prioritization?
• Can this bridge to *in vitro* transcriptomic-based risk assessment?
• Using NAMS to address data poor, high exposure chemicals (ECHA)
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Use of high-throughput, *in vitro* bioactivity data in setting a conservative point-of-departure (POD) will require **greater confidence** that *in vitro* bioactivity data, in concert with high-throughput toxicokinetic information and reverse dosimetry, can be used to estimate administered dose equivalents (ADEs) at or below the PODs derived from traditional animal studies.

*Partner Agencies EPA, ECHA, EFSA, A*STAR, Health Canada, NTP*
# Examining the utility of in vitro bioactivity as a conservative point of departure

<table>
<thead>
<tr>
<th>Partner</th>
<th>Primary roles/contributions</th>
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</table>
| EPA-ORD [NCCT, NCEA, and CSS] | • Lead/organizing partner  
• Contributed high-throughput toxicokinetic information, high-throughput screening information (ToxCast/Tox21) and their corresponding administered dose equivalents, point-of-departure information from in vivo studies.  
• Provided chemicals to A*STAR for additional screening in high-throughput assays. |
| ECHA             | • Compiling publicly available point-of-departure information from an IUCLID database of chemical registration information, with an emphasis on sharing information for chemicals with available high-throughput toxicokinetic information. |
| EFSA             | • Compiling point-of-departure and exposure information from registration dossiers with an emphasizing information for chemicals with available high-throughput toxicokinetic information. |
| A*STAR           | • Initiated bioactivity screen for 64 prioritized ToxCast chemicals in three organ-relevant (liver, kidney and lung) in vitro models.                                                                                          |
| Health Canada    | • Compiling exposure and point-of-departure information emphasizing information for chemicals with available high-throughput toxicokinetic information.                                                                         |
• Identify ~90 REACH-registered, “in vivo data-poor” chemicals with exposure information
• Identify ~40 “in vivo data-poor” chemicals with high throughput toxicokinetic data available
• Identify ~100 chemicals having 90-day or other repeated dose in vivo toxicity studies available with high throughput toxicokinetic data available
  – 35 chemicals with less conservative PODnam estimates, PODtraditional:PODnam ratio < 1;
  – 35 chemicals with a moderate PODtraditional:PODnam ratio between 1 and 2 (assumed moderate level of protection)
  – 35 chemicals with an overly conservative PODnam estimates, PODtraditional:PODnam ratio > 2
• Select ~10 chemicals for in depth in vivo assessments by NTP
  – 90 day toxicity studies with toxicokinetic measurements
  – Sequential assessments of transcriptomics in selected organs

*Study flow (in development)*

*Integrated APCRA case studies*
Thank you!

https://niehs.nih.gov
<table>
<thead>
<tr>
<th>Chemical Name</th>
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<tbody>
<tr>
<td>Furan</td>
<td>Thujone</td>
<td>Bisphenol AF</td>
</tr>
<tr>
<td>Diethylhexyl phthalate</td>
<td>Fenofibrate</td>
<td>Coumarin</td>
</tr>
<tr>
<td>Acrylamide</td>
<td>Bromodichloroacetic acid</td>
<td>Perfluorooctanoic acid</td>
</tr>
<tr>
<td>Tris(chloropropyl) phosphate</td>
<td>Hexachlorobenzene</td>
<td>Ethinyl estradiol</td>
</tr>
<tr>
<td>Triclosan</td>
<td>Tetrabromobisphenol A</td>
<td>Ginseng</td>
</tr>
<tr>
<td>Pentabromodiphenyl ether mixture</td>
<td>Pulegone</td>
<td>Milk thistle extract</td>
</tr>
<tr>
<td>3,3’,4,4’- Tetrachloroazobenzene</td>
<td>Methyleugenol</td>
<td></td>
</tr>
</tbody>
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Ongoing 5-day studies - data under review/reporting

- Decabromodiphenyl ether
- 2,2',4,4'-tetrabromodiphenyl ether
- Bis(2ethylhexyl) tetrabromophthalate
- Tetrabromobisphenol A bis(2,3-dibromopropyl ether)
- Hexachlorocyclopentadienyl-dibromocyclooctane
- Decabromodiphenylethane
- 2-Ethylhexyl diphenyl phosphate
- Tert-butylphenyl diphenyl phosphate
- Ginkgo biloba extracts (5)
- 2-Ethylhexyl-2,3,4,5-tetrabromobenzoate
- Hexabromocyclododecane
- Firemaster 680
- Triphenyl phosphate
- Isopropylated phenol phosphate
- Tricresyl phosphate
- Isodecyl diphenyl phosphate