

EU-ToxRisk Project and NCCT Capabilities



EU-ToxRisk – Tox21 Joint Meeting

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Office of Research and Development

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EU-ToxRisk Project and NCCT Capabilities

Highlighting today (very briefly) NCCT capabilities and projects that could be useful in collaborations with EU-ToxRisk

- Software and Database Development
- Two New Dashboards Cheminformatics & RapidTox
- Ongoing and New Modeling Efforts
 - Read Across with Uncertainties
 - Biological dynamics and Tipping Points
 - HTTK
 - Transcriptomics
 - In vitro metabolism retrofits

Database and Software Development

Users outside of NCCT (EPA + External) We have developed Dashboards RapidTox (Rapid Risk Assessment Prototype) a wide number of Chemistry (DSSTox + PhysChemDB + ...) databases that are ACToR (data on 500K chemicals in 1000s of sources) ToxCast (All ToxCast in vitro data) EDSP21 (data on endocrine assays for EDSP chemicals) **Dashboard Tools** Web services and APIs Databases DSSTox (chemistry – IDs and structure, 700 K chemicals) ACToR (risk-related data from 1000s of sources) PhyschemDB (physchem data, measured and predicted) ToxRefDB (detailed in vivo data) code-assisted InVitroDB (ToxCast in vitro data) and manual ToxValDB suite (summary in vivo data from multiple sources) curation LitDB (literature information on chemicals) PKDB (Pharmacokinetics data and model parameters) RapidToxDB (project-level data for RapidTox dashboard) ScrubChem (machine-annotated version of PubChem)

Pis + Postdocs – Science projects

use to drive

Cheminformatics – The New Comptox Dashboard

- ~720,000 chemicals
 - With quality metric scores
- >10 years assembling data
- Physchem properties
- Use and composition information
- Mass spec data
- Structural, formula, mass spec searching
- Downloading search outputs

| | ed States ironmental Protection ncy | Home Advanced | I Search | | | | Search (| CompTox Dashboard | Q | Optio |
|---|---|------------------|-------------------|---------------------|-------------------------------|------------------|-------------------|----------------------|---------|-------|
| | | | | | | | | Submit Comment | Share - | Сор |
| | Bisphenol A 80-05-7 DTXSID70 | 120182 | | | | | | | | |
| 9 | Searched by Appro | oved Name: Found | d 1 result for 'b | isphenol A'. | | | | | | |
| | Q 🔟 🖪 🚣- | Q. | _ | | | | | | | |
| | | | | Intrinsic Properti | es | | | | | |
| | H ₃ C. | CH ₃ | | Molecular Fo | rmula: C15H16O2 | | | Q Find All Chemicals | 6 | |
| | | | | Average Mas | s: 228.291 g/mol | | | | 6 | |
| | | \sum | | Monoisotopio | : Mass: 228.115030 g/i | mol | | [| 0 | |
| | | L | | Structural Identif | iers | | | | | |
| | HO | OH | | Record Informati | on | | | | | |
| | | | | | | | | | | |
| | 2 | | | | | Contraction 11 2 | | | | |
| | Chemical Properties | External Links | Synonyms | Product Composition | ToxCast in Vitro Data | Exposure A | nalytical PubChem | Comments | | |

https://comptox.epa.gov

RapidTox Dashboard

- Goal: Enable <u>screening-level assessments</u> to be performed for hundreds to thousands of chemicals as part of a tiered approach
- Integrates data on chemical properties, fate and transport, hazard, and exposure through an interactive on-line dashboard

Tiered approach

- High Tier Access to high-quality data as inputs to risk assessments, when available (e.g., IRIS, RfDs)
- Lower-Tier access lower-tier data when higher-tier is not available (e.g., PPRTVs, in vivo and in vitro data)
- Develop and provide modeled inputs when lower-tier data in not available



RapidTox Dashboard

| Environme Agency | intal Protection Home Cor | mpTox Dashboard | • | | | | | | | | | | | Search | CompTox | Dashboard |
|-----------------------------|--------------------------------|--|---------------------------|--------------------------------------|-----------------------|--------------|--------------|---------------|----------------|-----------------------------|------------|-----------------------------|-----------------------------|----------------|----------------|----------------|
| | | | | | | | | | | | | | | Submit C | Comment | Share - |
| DanidTa | av Accessment | | | Mode-of- | Action/Adverse Outcom | ne Pathway | | | | Pharmacokinetic | 5 | | | | | |
| каріатс | DX Assessment | | | Biologica | I Selectivity | Concentral | tion Respor | ise Data | | Level 1: In Vivo S | tudies | - 1 | Level 2: High- | -Throughput | t Pharmacoki | inetics |
| CI | CI CI CI | erties | Environmental Fate/Tra | sport ¥ | | | 1 | -n (| | | | 1 | Fub | Renal C | learance | Met. Stability |
| 0 | | Persistence activities Trans (Salitie) | 8 - mt- | minita mediatala 8 - mediatala | | | | | None Available | | | 0.692 | 4.64 | | 9.612 | |
| | | 10 | because her mental | 000 | x Pedian 27 | F | | 1-1 1 <u></u> | - | | | | Css/OE (Median) | Css/OE | (Upper) | Css/OE (Lower) |
| ci 🦯 | Point of Departure E | stimate | | Forrest Plo | est Plot | | | | | Point of Departure Estimate | | | Forrest Plot | | | |
| hemical X | Mathead | | 1050 | Г | | | | | = | Method | | LD50 | 1000 | | | |
| | Method | | (0.50 | 1000 | | | | | | In Vivo (Acute) | | (mg/kg) 50 | | | | |
| | In Vivo (Acute) | | (mg/xg) | | | | | | lance | Method | | POD (mg/kg/d) | 200 | | | |
| ezero ivel 1: In Vi | in vivo (Acute) | | ~ | | 1 | | | | 3 | In Vivo (Chronic) | | 4.0 | No. | | | |
| | Method | | POD | 300 | | | | | 11., | In Vitro Assay | | 0.2 | 0000 | - | | 1 L |
| tule | | | (mg/kg/d) | N | ſ | | | | et al., | In Vitro Assay (AOP-de | erived) | 0.5 | 1 | | | |
| nhalation Drai | In Vivo (Chronic) | | 4.0 | 51 | | | | | | QSAR | | 2.0 | - | | . 1 | |
| Feed Other ubacule | | | | <u><u></u><u></u><u></u><u></u></u> | | | | | | Provide America | | 2.0 | 0.1 In Vhe | o In Vivo In 1 | Vitro AOP | QSAR RA |
| nhalation Drail | In Vitro Assay | | 0.2 | 8 <u>8</u> | t | | L | - | | Acids Acidss | | 5.0 | (Acute |) (Chronic) | | |
| oed her abchronic | In Vitro Access (AOD-decise | d) | 0.5 | 1 | | | | | | Assessment Sum | mary | 1.0.0 | | | 115 | 1.000 |
| nhalation Deal | In vitro Assay (AOP-berive | u) | | | | | | | | Chamical Salastivity | | Value | | Confidence | Urs | RTD |
| Other Strenic Non- | OSAR | | 20 | | | | | | | Likely Hazards: | | Liver toxicit | v | High | | |
| ancer inhalation | | | | 0.1 | | | | | | Likely AOP/MOA: | | PPARA rece | , ptor activation | High | | |
| Feed Other | Devel Arrest | | 2.0 | In | Vivo In Vivo I | in Vitro AOP | QSAR | RA | | Point-of-Departure Es | timate | causing heps 4.0 mg/kg/c | atocyte prolif | | X-X-X-X | 0.04 mg/kg/d |
| hronic Cancer nhalation | Read Across | | 3.0 | (A | icute) (Chronic) | | | | | RapidTox Screen | ing Levels | | | | | |
| Feed Other | | | | | | | | | -111 | Resident Soil (mg/kg) | 7.5 | Resident Air | r (ug/m ³) 0.1 | 15 | Tap Water (ug/ | L) 1.1 |
| | Assessment Summar | ry | | | | | | | | Industrial Soil (mg/kg) | 33 | Industrial Ai | ir (ug/m ³) 0.6 | 6 | | |
| | Value | | | | Confidence UFs RfD | | | | | Comments | | | | | | |
| | | | | | | | | | - | | | | | | | |
| | Chemical Selectivity: Moderate | | Moderate | | Moderate | | | | | | | | | | | |
| | Likely Hazards: | | Liver toxicity | | High | + | + | | | | | | | | | |
| | 12-1-00/0404 | | DDADA | 00404 | | + | + | | | | | | | | | |
| | Likely AOP/MOA: PP | | PPARA receptor activation | | nign | | | | | | | | | | | |
| | Paint of Departure Estimat | Point-of-Departure Estimate 4.0 ms/ks/d | | tocyte prolif | | X-X-X-X | 0.04 | me/ke/d | -11 | | | | | | | |
| Point-or-Departure Estimate | | le la | 4.0 mg/kg/d | | | A-A-A-A | 0.04 mg/kg/d | | | | | | | | | |
| | RapidTox Screening Levels | | | | | | | | | | | | | | | |
| | Resident Soil (mg/kg) | 7.5 | Resident Air | (ug/m ^a) | 0.15 | Tap Water (u | g/L) | 1.1 | | | | | | | | |
| | | 1 | 1 | | | 1 | | 1 | | | | | | | | |
| | Industrial Soft (see 0) | 22 | Industrial Al- | (| 0.6 | | | | -11 | | | | | | | |

Not yet publically released

6



Uncertainty and Read-Across

- A major uncertainty in Read-Across models is that *development and* acceptance is very context dependent and based on subjective expert judgement.
- There is no harmonized approach to ensure er reproducible decisions

Critical need is an objective measure of uncertainty in a read-across prediction









Predicted to be harmful

- Reliable data
- Missing data



Office

Development

of

Quantitatively Evaluating Read-Across Uncertainty



Read-across approach will allow users to define similarity and analog cut-offs while trading off uncertainty

Patlewicz et al., In Review



Evolution of High-Throughput Toxicokinetics



<u>Present</u>

- Steady-state IVIVE models for hundreds of chemicals based on limited high-throughput *in vitro* assays
- Monte carlo methods incorporate inter-individual variability
- Structure-based methods to estimate tissue partitioning
- HT-Physiologically-Based Pharmacokinetic (HT-PBPK) models for hundreds of chemicals

<u>Planned</u>

- Computational framework to compare IVIVE with *in vivo* data and allow explicit estimates of uncertainty
- Distinguish chemical classes where we do good and poor job of predicting pharmacokinetics



Ongoing Transcriptomics @ USEPA

 Technical & contractual evaluation of 3 technologies providing whole genome transcriptomics (Omega Low Coverage and Targeted & BioSpyder Temp-O-Seq)



Technical Performance Equal

Functional Performance Not Equal for Positive Controls

- BioSpyder awarded contract based on functional performance and cost
- Currently engaged in pilot study to validate workflow and refine experimental design





- High-throughput transcriptomics will fundamentally change the way we evaluate chemicals for safety
 - Greater coverage of biological space
 - Reduced cost
 - Ability to leverage large existing databases of gene expression data
 - Fits logically in a tiered testing approach
 - Allows dose- and time-response characterization
- Optimization & operationalization underway pilot study to validate workflow and refine experimental design
- Challenges remain:
 - Cell type/line selection
 - Data handling and processing
 - Optimal data analysis procedures

Retrofitting Assays for Metabolic Competence – Extracellular Approach

Alginate Immobilization of Metabolic Enzymes (AIME)





XME Activity in Microspheres



Small Molecule Inhibition of XME Activity



In Vitro Data – What is Adverse?

- What data from in vitro assays do we use as the point of departure for hazard assessments?
- How to discriminate between compensatory changes from changes that will (might) lead to adverse outcomes?
- □ **Tipping Point**: Threshold between adaptation and adversity



□ Can we use **Tipping Point** to define a point of departure (PoD) for risk assessment ?

Use ToxCast High Content Imaging (HCI) data to identify Tipping Points



- 967 chemicals (ToxCast)
- HepG2 cells culture
- 10 concentrations
- 3 Time points
- 10 HCI Assays
- 400 plates
- 100,000 wells
- 2,400,000 images

Tipping Point Analysis



Shah et al Environ Health Perspect 124:910–919; http://dx.doi.org/10.1289/ehp.1409029





Grace

EU-ToxRisk - Tox21 NCCT Team



Kevin



Matt

We look forward to productive discussions and generating some great ideas for collaborative case studies



Richard