CLiCC (Chemical Life Cycle Collaborative) Network for Rapid Assessment of Chemical Life Cycle Impact
CHEMICAL LIFE CYCLE COLLABORATIVE: CHEMICAL PROPERTIES MODULE

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Extending search of QSARs to more endpoints:

- Carcinogenicity (more quantitative)
- Developmental toxicity
- Reproductive toxicity
- Cardiovascular toxicity
- Dermatotoxicity
- Endocrine toxicity
- Epigenetic toxicity
- Genotoxicity

- Hematotoxicity
- Hepatotoxicity
- Immunotoxicity
- Musculoskeletal toxicity
- Neurodevelopmental toxicity
- Neurotoxicity
- Ocular toxicity
- Respiratory toxicity
- Skin sensitization
Evaluating proxies for natural resource and economic considerations

Jaye Harada
Current abiotic resource depletion methods do not evaluate all aspects of scarcity
- supply risk
- depletion rate
- ore grade decrease

Three goals for module:
- Calculation of existing abiotic resource depletion characterization factors for new inorganic materials
  - **User can choose which method(s) to use** to evaluate a material's scarcity
- Integration of future resource demand and production scenarios to calculate future-oriented characterization factors
  - These factors will be limited to reserve-based and production-based methods
- **Evaluate uncertainty** in USGS production and reserves data
  - Consider year-to-year variance in USGS assessments
Potential exposure models at different levels

Dr. Dingsheng Li (new CLiCC project member)

Past work and ideas for the future
Introduction

- Why do we need exposure models

Environmental fate of chemicals

Human health impact assessment
Models at different levels

- Long-range exposure models
  - Traditionally employed in life cycle impact assessment (LCIA)
  - Can be improved for specific categories of chemicals

- Close-range exposure models
  - Indoor exposure
  - Personal care products

- Internal organ specific exposure model
  - Potential use of physiologically based toxicokinetic (PBTK) model
  - Linking target organs with toxic effects of chemicals
  - Much more complex than the other two

Introduction
Long-range exposure
Input parameters

- **Inhalation:**
  - Concentration of chemical in the air (from Fate & Transport module)
  - Inhalation rate of the population (from EPA exposure handbook, can be adjusted for sensitive population)
  - Population size (pre-defined, scenarios)

- **Ingestion from water:**
  - Concentration of chemical in the water (from Fate & Transport module)
  - Ingestion rate of water (from EPA exposure handbook, can be adjusted for sensitive population)
  - Population size (pre-defined, scenarios)

- **Ingestion from food:**
  - Concentration of chemical in the water and agricultural soil (from Fate & Transport module)
  - Bioconcentration factors, biotransfer factors, etc. (from previous empirical models, need support from QSAR for calculations)
  - Ingestion rate of different produces (from established databases, can be differentiated to different age groups)
  - Population size (pre-defined, scenarios)
**Output parameters**

- **Intake amount**
  - Expressed in mass (kg) or dose (mg/kg-day)
  - Can be converted to intake fractions (kg\text{intake}/kg\text{emitted})
  - Used to estimate human toxicity impact
  - Requires either epidemiology data or chronic *in vivo* animal toxicity data, which can be supported by QSAR module
Most suitable for

- Chemicals emitted to the general environment
  - Byproducts, pollutants, pesticides, etc.
  - No need to address indoor exposure/dermal exposure

- For chemicals with relatively limited physico-chemical data
  - Missing data can be generated from the QSAR module or Fate & Transport module

Long-range exposure
Example

Long-range exposure
Close-range exposure
Input parameters

- **Inhalation:**
  - Removal and degradation rates (from indoor air model [Wenger et al., 2012])
  - Inhalation rate of the population (from EPA exposure handbook, can be differentiated to different age groups)
  - Indoor room descriptions: ventilation rate, volume, occupants, temperature, etc. (pre-defined, scenarios)

- **Dermal exposure:**
  - Contact duration (pre-defined, scenarios, data from industry)
  - A series of permeability and transfer rates (QSAR, Berg 2009)
Output parameters

- **Intake fractions**
  - Expressed in fractions \( \frac{\text{kg}_{\text{intake}}}{\text{kg}_{\text{emitted}}} \)
  - Usually orders of magnitude higher than iF of the same chemicals released to the general environment
  - Used to estimate human toxicity impact, with support of emitted/applied mass (user input)
  - Requires either epidemiology data or chronic *in vivo* animal toxicity data, which can be supported by QSAR module
Most suitable for

- **Chemicals emitted to the indoor environment**
  - VOCs that are released from products used indoors
  - Occupational setting

- **Chemicals used in personal care products**
  - Directly applied to skins such as shampoo, lipsticks, lotions, etc.
  - Data about how the products are used is essential
Example

Chemicals

Close-range exposure
Example

Time [hr]

0.0001 0.001 0.01 0.1 1 10

0.0001 0.001 0.01 0.1

high volatility, high skin permeability

low volatility, low skin permeability

Close-range exposure

4 min 8 hrs

iF

0.0001
Internal organ specific exposure
Input parameters

- **Human physiology data:**
  - Body weight, organ weights, cardiac output, etc.
  - Existing literature, can be adjusted for sensitive population

- **Exposed amounts:**
  - Concentration of chemical in air/food (from Fate & Transport module)
  - Inhalation rate and ingestion rates (from USEtox refs, EPA exposure handbook)

- **Inside body kinetics (most challenging):**
  - Adsorption (from existing QSAR type models: Caco-2, PAMPA, etc.)
  - Distribution (from existing database, potential QSAR models)
  - Metabolism (from existing database)
  - Excretion (from existing models)
Output parameters

- Concentrations in blood and various organs
  - Can be converted to cumulative amounts in blood and various organs over time
  - Compare with high throughput in vitro toxicity tests
  - Can be independent on epidemiology/animal tests, opening up much wider toxicity dataset
  - More accurate representation of internal dose – given the data and model are good (otherwise, garbage in garbage out)
Most suitable for

- **Chemicals that require higher accuracy or dynamic of exposure**
  - Can predict doses in sensitive organs at different ages

- **Chemicals without epidemiology/animal toxicity data**
  - Can use other data sources for human health impact assessment

- **Chemicals with richer physiological kinetic data**
  - Linked with QSAR models, the data gap in the ADME parameters may be closed

*Internal organ specific exposure*
Example

Internal organ specific exposure
More of a field of research

- No “generic” PBTK model exist yet
  - The community in toxicology is still working on this topic
  - Mostly due to the complexity of different chemicals kinetics inside the body

- No attempt to link PBTK with LCIA has been made
  - Cross disciplinary may LCIA be, PBTK is still untouched by LCIA researchers

- More complex model, more computation time
  - Even the most basic PBTK model is much more complex than the other exposure models
  - Complexity similar to multimedia environmental fate models
  - Therefore takes more computation power
  - More complexity usually leads to more uncertainty, too
Summary

- Three models addressing different scales of exposure/output are being considered for further development and integration into CLiCC framework
- User would have the option to determine which one to use based on their need
- Ranking of readiness:
  - Long-range exposure models (easy after F&T model fully developed)
  - Close-range exposure models (relatively easy after F&T model fully developed)
  - Internal organ specific models (requires more complex PBTK modeling & QSARs for internal body parameters)

Conclusions
APPLICATION OF THE CLiCC TOOL
Characterization of uncertainty is very important
- Identification of uncertainty “hotspots”
- Stochastic representation (probability distributions)

Outputs provided for individual modules (not just entire CLiCC Tool results)
- First round of case studies: individual modules to determine feasibility and guide output visualization

Most users will be relatively technical and LCA literate

Need to be transparent about data sources
- Will provide output identifying the data sources used in each module for a given chemical run through the CLiCC tool
CLiCC Tool Architecture

1. Background LCI DB
2. Predicted LCI
3. Production Module
4. F&T Module
5. Tox Risk Module
6. Toxicity DB & QSARs Module
7. LCIA Calculation Module
8. Visualization Module

- Indirect & external CFs
- Energy, water, solvents
- HHI, exergy
- Scarcity Module

Chem Structure

- Chem Structure
- Reactions kinetics conditions
- Production rates (market size)

User Info

- Production Module
  - User Info
  - Geog. DB
  - Energy, water, solvents

- F&T Module
  - User Info
  - Energy, water, solvents
  - Geog. DB
  - Energy, water, solvents

- Tox Risk Module
  - User Info
  - Energy, water, solvents
  - Geog. DB
  - Energy, water, solvents

- Visualization Module
  - User Info
  - Energy, water, solvents
  - Geog. DB
  - Energy, water, solvents
Chemical Synthesis & Production Module

**INPUTS**
- Reaction kinetics
- Chemical formula
- Operating ranges
- Scale
- Upper/lower flammability limits
- Any other process constraints

**OUTPUTS**
- Raw material requirements (molar or mass)
- Production rates for product, by-product, waste
- Upper bound on selectivity
- Minimum energy requirements (next step in module development)
SMILES
(simplified molecular input line entry system)
unique identifier for a given chemical that can be derived from its chemical structure, chemical name, or CAS number

Predictive Life Cycle Inventory (LCI) Module

INPUTS -> Artificial Neural Networks -> OUTPUTS

Cumulative Energy Demand (CED)
Water requirements
Global Warming Potential (GWP, CO2 equivalents)
QSAR Module

**Inputs**

**SMILES**
(simplified molecular input line entry system)
unique identifier for a given chemical that can be derived from its chemical structure, chemical name, or CAS number

**Outputs**

**Physico-chemical Properties**
Environmental Fate Properties

**Ecological Effect**
Fathead Minnow LC50 96hr, Daphnia Magna LC50 48hr, Oral Rat LD50

**Human Health Effect**
Developmental Toxicity, Mutagenicity, Carcinogenicity, Skin Irritation
Thank you!