Expanding the Applicability Domain of the Chemical Activity Approach for Hazard and Risk Assessment

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Introduction:

- Various sources of information are used for chemical assessment, e.g., in vitro, in vivo, in situ, in silico, including an array of units and media.
- Converting data to consistent units of chemical activity (*a*) can facilitate the interpretation and application of information for hazard and risk assessment:
  - **Figure 1**: Combining effect and exposure data for risk and safety assessment [1]
  - **Figure 2**: Examining toxicity data to identify baseline toxicants and possible Mode of Action (MOA) classifications [2] and for addressing chemical mixture toxicity [3]
  - **Figure 3**: Improving comparisons of in vivo toxicity endpoints across species [4,5]
  - **Figure 4**: Incorporating high-throughput in vitro toxicity data [6]
- Acute median lethal baseline toxicity for neutral organic chemicals expressed in terms of chemical activity (La_{50}) is generally consistent across species: 0.05 (range ~0.01 – 1.0) and for chemicals that exert more specific MOA, La_{50} is usually < 0.01
- However promising, case studies using the approach are limited and the concept is not routinely considered

What is chemical activity (*a*)?

- Chemical activity relates to chemical potential, fugacity and concentration [1].
- Chemical activity (*a*) quantifies the energetic level of a chemical relative to a chosen reference state:
  e.g., $a_{Water} = C_{Water}/C_S$, where C_{water} is the dissolved concentration and C_S is the solubility of the liquid substance in water;
  e.g., $La_{50} = LC_{50}/C_S$, where La_{50} is the median lethal activity and LC_{50} is the median lethal exposure concentration.
- *a* is the fraction of saturation of the liquid-state chemical; measurement scale ranges from 0 (no chemical) to 1 (saturation).
- Chemical activity is an equilibrium criterion, when equilibrium occurs, *a* is the same in all phases and compartments.

LRI ECO.30 Project Objectives:

Further examine the chemical activity hypothesis for toxicity and risk assessment

Figure 1: Risk and safety assessment (e.g. PBDE 99) [1]

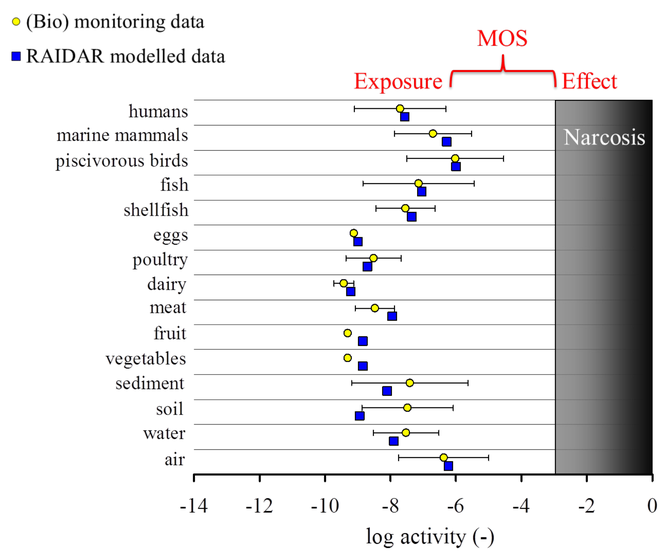


Figure 2: MOA classification [2] and mixture toxicity [3]

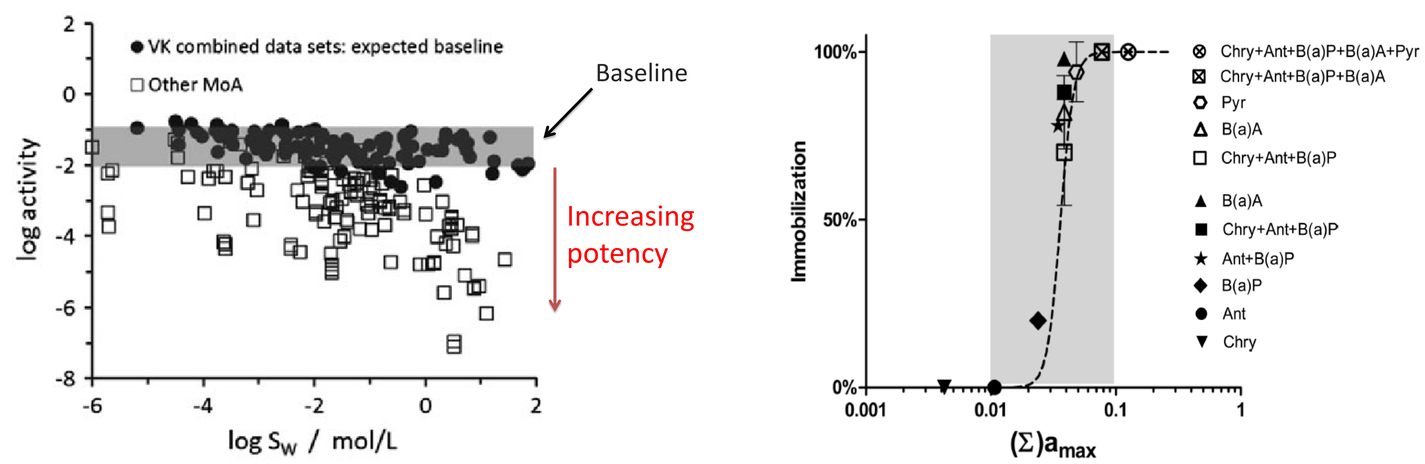


Figure 3: Establishing lethal [1] or effective [4] a_{50} from in vivo testing data

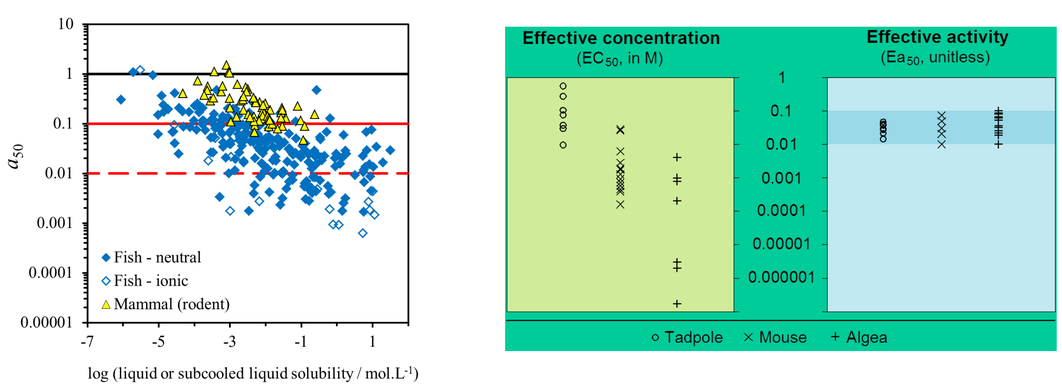
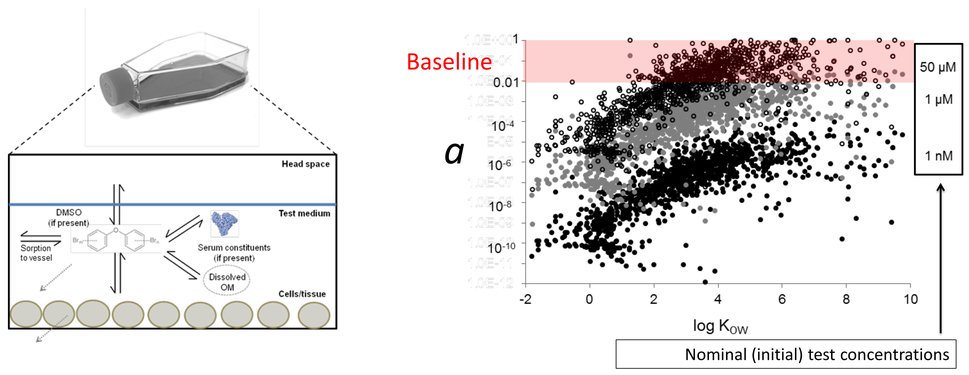


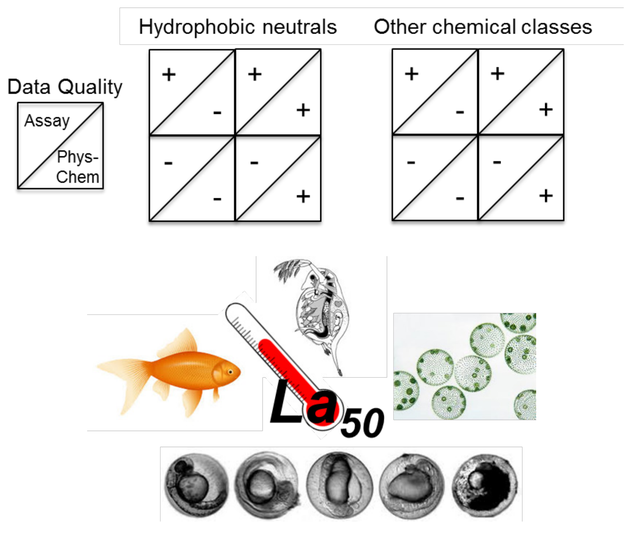
Figure 4: Estimating chemical activity from high-throughput in vitro toxicity and bioactivity tests [5]



General Methods:

- Compile and evaluate toxicity testing & physical-chemical property data and apply the chemical activity approach as case studies e.g., various species and test systems including in vivo & in vitro data comparisons, acute & chronic exposures, evaluate the chemical domain of applicability (chemical classes), different MOA, different endpoints

Compile toxicity data from available databases and perform QA/QC	• ECOTOX, REACH, EFSA and UBA dossiers, other sources • Categorize: high, medium, low confidence
Compile property data and perform QA/QC	• REACH and EFSA dossiers, property handbooks, QSAR models • Categorize: high, medium, low confidence
Express toxicity data using chemical activity	• External concentration-based chemical activity calculations (equilibrium) • Internal concentration-based chemical activity calculations (toxicokinetic models)
Intercomparison of chemical activity & clustering by MoA	• Compare chemical activities across different chemicals, tests and species • Explore clustering and ranges of activity-based Toxic Ratios by MoA



On-Going Research Activities, Datasets:

1. **In vivo, juvenile + adult, acute + chronic**
   - Fish data (78,206 records, 3,032 chemicals) from 4,011 studies
   - Mollusc and Crustacean data (39,955 records, 2,469 chemicals)
   - Amphibian and Reptilian data (7,172 records, 554 chemicals)
   - Invertebrates and other miscellaneous species data (21,117 records, 1,576 chemicals)
2. **Acute Fish Embryo Tests (FET)**
3. **Chronic fish toxicity (Fish, Early Life Stage Toxicity, FELST)**
4. **Chronic algal tests**
5. ***C. elegans* (nematode), *A. fischeri* (bacteria)**
6. **In vitro, bioassay (e.g., ToxCast)**

References:

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