TOXCAST/TOX21: MODERN APPROACHES FOR INDUSTRY BENEFIT

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For all Unilever presentations see: www.TT21C.org
INDUSTRY VIEW ON TOX21/TOXCAST

• 35-40% consumer product and chemical company ingredients in Tox21
THE CONSUMER IS KING/QUEEN
TT21C RIVER ANALOGY

Before and after images showing the impact of traditional toxicity testing on a river environment.
INTERPRETATION OF NAS TT21C

High-throughput screening

Focused pathways approach

Food for Thought ...


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Exposure assessment → Chemico-informatics → Connectivity Mapping

Pathway inference

In Vitro Pathway BPAD ← Pathway Modelling ← High Throughput Screening

Pathway characterisation

Biokinetic Modelling ← QIVIVE

Pathway-based risk assessment

Human/Environment Safety Assessment
PERSONAL CARE CONSUMER PRODUCTS INDUSTRY CAN BE SUCCESSFUL IN THIS

1. Chemical ingredients not generally intended to be pharmacologically active (compare Pharmaceutical Co.)
2. Low bioavailability and often topical exposure
3. Open regulatory environment

• Making an exposure-led safety decision based on confidence that the safe level is within or below the adaptive homeostasis response, captured by appropriate in vitro systems and complemented with network computational models
The TT21C framework begins with a chemical ingredient with ‘significant’ human exposure. This chemical is then subjected to in vitro high-throughput screening (HTS) for pathway inference and chemical profiling (chemo-informatics) to define tox-pathway(s) of concern. This process leads to in vitro biokinetics & free concentration determination, which is then used to calculate in vitro adversity, point of departure (POD/BPAD) concentration determination.

The framework also considers computational systems biology models and in vitro concentration response in appropriate assays. From this, an in vivo human safety estimate (mg/kg/day) is calculated. Additionally, biokinetic model (QIVIVE) and QSPR/in vitro physicochemical parameters are utilized to further assess the safety and effects of the chemical.

Chemical ingredient with 'significant' human exposure

**Tier 1:** Exposure based waiving

- *In vivo* HTS (pathway inference)
- Chemical profiling (chemo-informatics)

**In vitro** biokinetics & free concentration

**In vitro** adversity, point of departure (POD/BPAD) concentration determination

**In vitro** concentration response in appropriate assays

**In vivo** human safety estimate (mg/kg/day)

Defined tox-pathway(s) of concern*

Biokinetic model (QIVIVE)

QSPR/*in vitro* physicochemical parameters

1. Generic stress/toxicity pathways
2. Specific receptor-mediated pathways
TT21C

- Chemical ingredient with ‘significant’ human exposure

  - Computational systems biology models
    - *In vitro* HTS (pathway inference)
    - Chemical profiling (chemo-informatics)

  - Tier 2: MIE/Pathway identification
    - Defined tox-pathway(s) of concern*
      - *In vitro* biokinetics & free concentration
        - *In vitro* adversity, point of departure (POD/BPAD) concentration determination

- *In vitro* concentration response in appropriate assays
  - *In vivo* human safety estimate (mg/kg/day)
  - Biokinetic model (QIVIVE)
  - QSPR/*in vitro* physicochemical parameters
Chemical ingredient with ‘significant’ human exposure

In vitro HTS (pathway inference)

Chemical profiling (chemo-informatics)

Tier 2: MIE/Pathway identification

1. Generic stress/toxicity pathways
2. Specific receptor-mediated pathways

Defined tox-pathway(s) of concern*

In vitro biokinetics & free concentration

In vitro adversity, point of departure (POD/BPAD) concentration determination

ToxCast™

Tox21

Computational systems biology models

In vitro concentration response in appropriate assays

In vivo human safety estimate (mg/kg/day)

Biokinetic model (QIVIVE)

QSPR/in vitro physicochemical parameters
Chemical ingredient with ‘significant’ human exposure

**In vitro** HTS (pathway inference)  
**Chemical profiling** (chemo-informatics)

**Defined tox-pathway(s) of concern***

**In vitro** biokinetics & free concentration

**In vitro** adversity, point of departure (POD/BPAD) concentration determination

**Tier 3:** BD/BK safety assessment

**Biokinetic model** (QIVIVE)

**QSPR/in vitro** physicochemical parameters

**In vivo human safety estimate** (mg/kg/day)

**Computational systems biology models**

**In vitro** concentration response in appropriate assays

1. Generic stress/toxicity pathways
2. Specific receptor-mediated pathways
Chemical ingredient with 'significant' human exposure

In vitro HTS (pathway inference)  Chemical profiling (chemo-informatics)

Defined tox-pathway(s) of concern*

In vitro biokinetics & free concentration

In vitro adversity, point of departure (POD/BPAD) concentration determination

In vitro concentration response in appropriate assays

Computational systems biology models

In vivo human safety estimate (mg/kg/day)

Biokinetic model (QIVIVE)

QSPR/in vitro physicochemical parameters
TOXCAST/TOX21 NEXT STEPS FOR INDUSTRY

- Core early tier screening tools
  - Sensitivity analysis?
- Advance the bioreactivity understanding wrt. **exposure**
- BPADs with RTK towards safety assessment or prioritization
  - QIVIVE/MoE ‘size’ questions – declining conc/limited AUC in vitro *cf.* steady state conc/infinite AUC in vivo?
- Characterise and communicate the variability and uncertainty
  - Not uncertainty factors
- Not forgetting: metabolism in *in vitro*
- Wetmore’s Wholesome Vegetables™ (@SOT/ICCA) – understand context
  - Human Phenomonitoring (Rusty Thomas)

*Courtesy of Barbara Wetmore:*
THANK YOU