



TOXCAST/TOX21: MODERN APPROACHES FOR INDUSTRY BENEFIT

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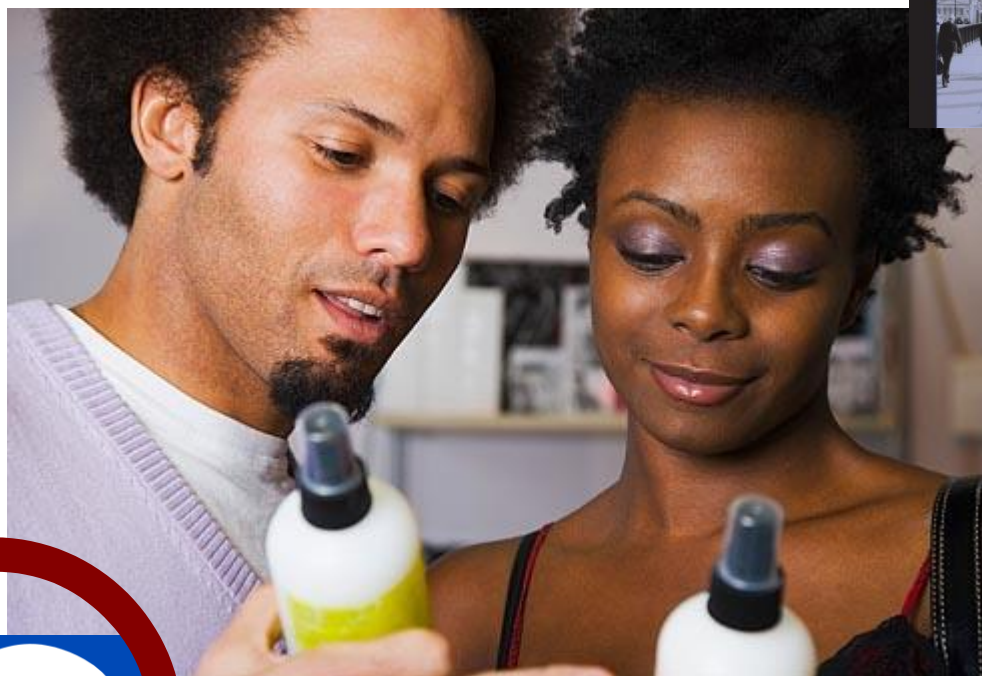
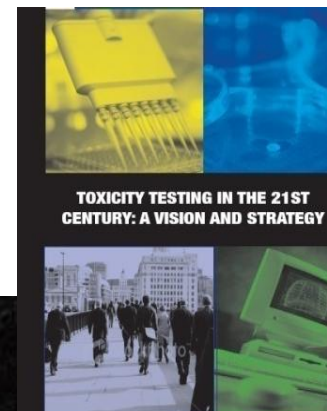
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INDUSTRY VIEW ON TOX21/TOXCAST

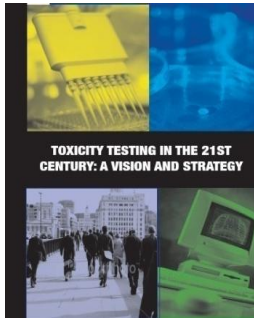


- 35-40% consumer product and chemical company ingredients in Tox21

THE CONSUMER IS KING/QUEEN



TT21C RIVER ANALOGY

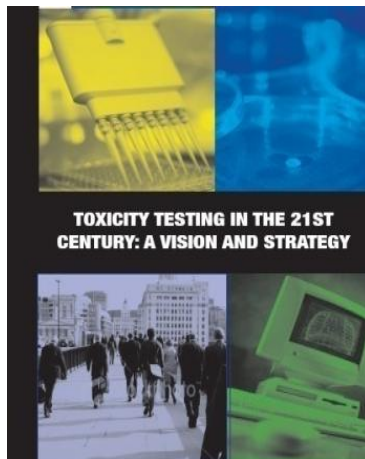


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Traditional toxicity testing



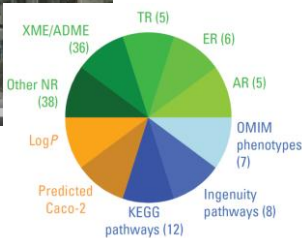
INTERPRETATION OF NAS TT21C



High-throughput screening

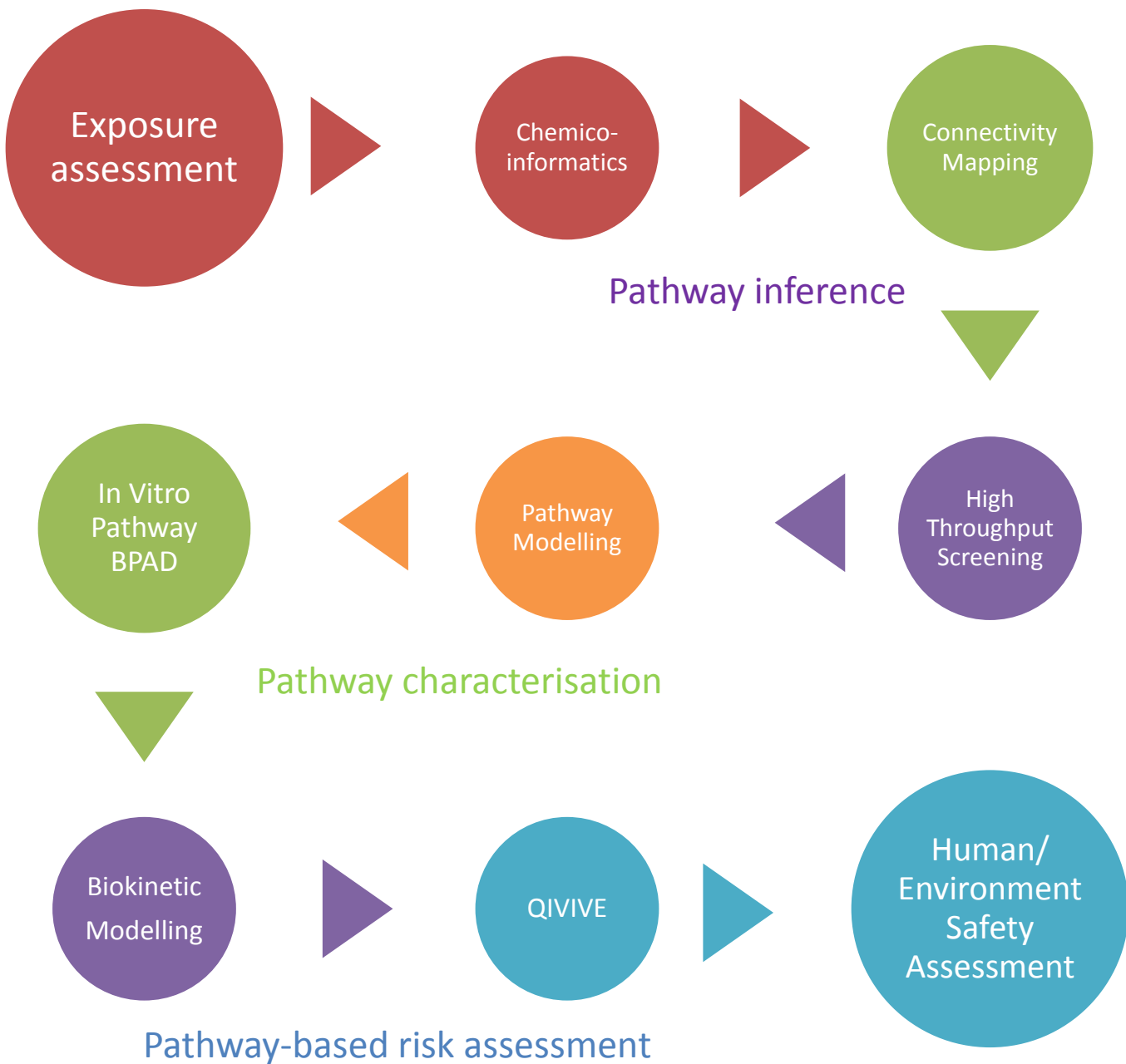
Focused pathways approach

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Food for Thought ...
Can Case Study Approaches Speed Implementation of the NRC Report: "Toxicity Testing in the 21st Century: A Vision and a Strategy?"
Melvin E. Andersen¹, Harvey J. Clewell, III², Paul L. Carmichael², and Kim Boekelheide³
¹The Institute for Chemical Safety Sciences, The Hamner Institutes for Health Sciences, Research Triangle Park, NC, USA; ²Safety and Environmental Assurance Centre, Unilever, Sharnbrook, Bedford, UK; ³Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, USA



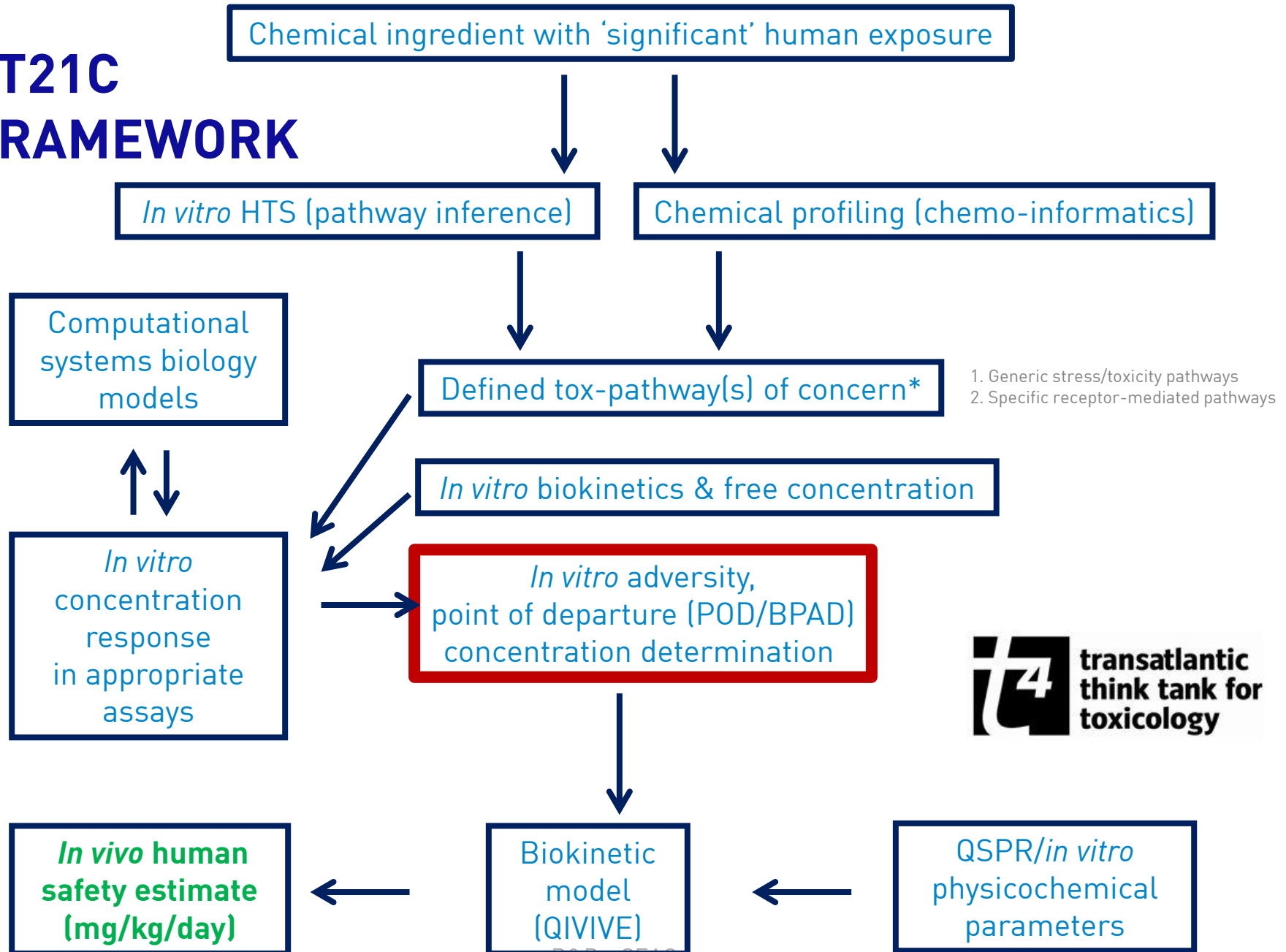


PERSONAL CARE CONSUMER PRODUCTS INDUSTRY CAN BE SUCCESSFUL IN THIS



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

TT21C FRAMEWORK



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Chemical ingredient with 'significant' human exposure

**Tier 1:
Exposure based waiving**

In vitro HTS (pathway inference)

Chemical profiling (chemo-informatics)

Computational systems biology models

Defined tox-pathway(s) of concern*

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

In vitro biokinetics & free concentration

In vitro concentration response in appropriate assays

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

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

Biokinetic model (QIVIVE)

QSPR/*in vitro* physicochemical parameters

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Chemical ingredient with 'significant' human exposure

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Chemical profiling (chemo-informatics)

**Tier 2:
MIE/Pathway identification**

Computational systems biology models

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ToxCast™



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Chemical profiling (chemo-informatics)

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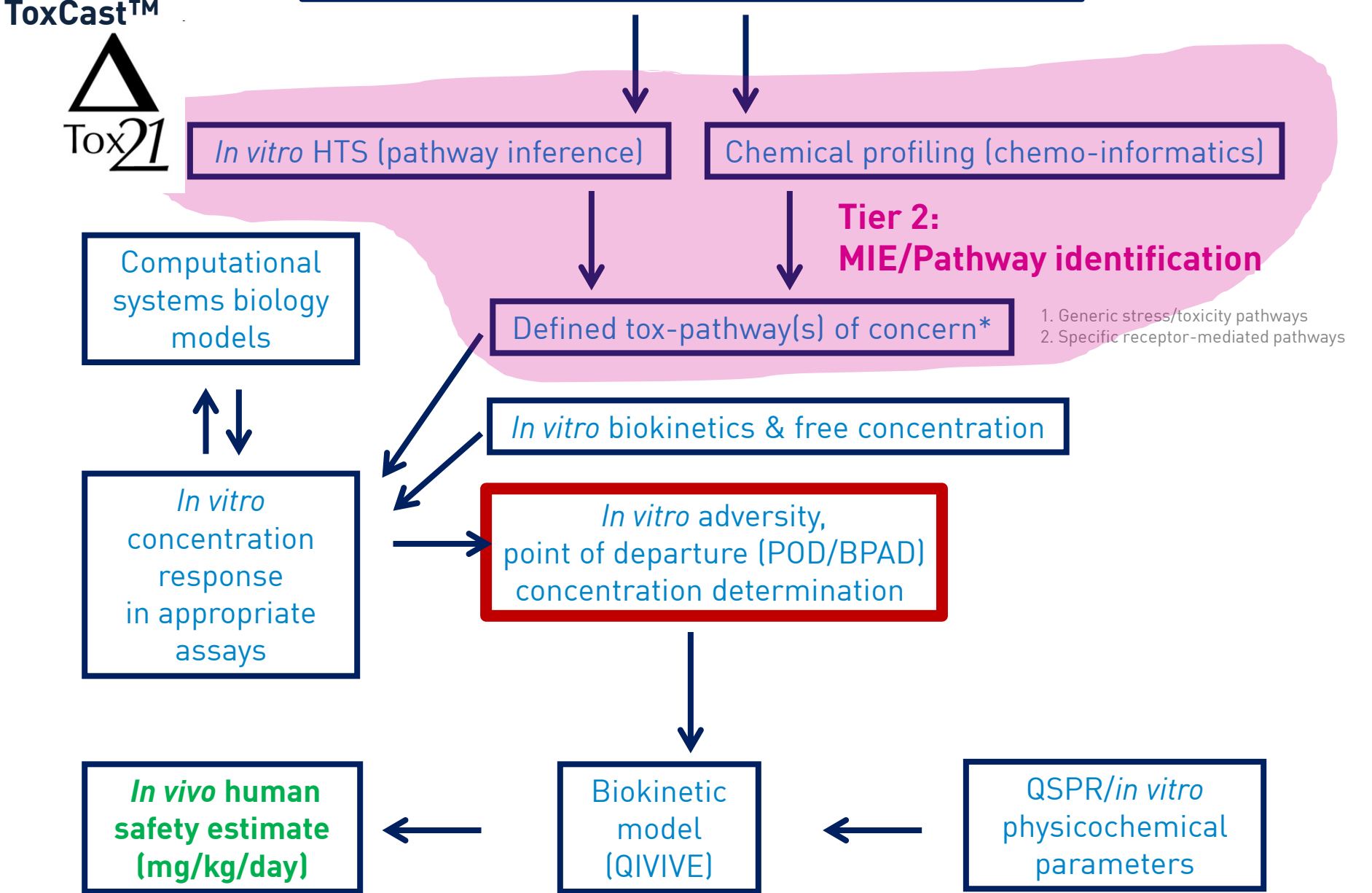
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**Tier 3:
BD/BK safety assessment**

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

Biokinetic model (QIVIVE)

QSPR/*in vitro* physicochemical parameters

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Chemical ingredient with 'significant' human exposure

In vitro HTS (pathway inference)

Chemical profiling (chemo-informatics)

Computational systems biology models

Defined tox-pathway(s) of concern*

In vitro biokinetics & free concentration

In vitro concentration response in appropriate assays

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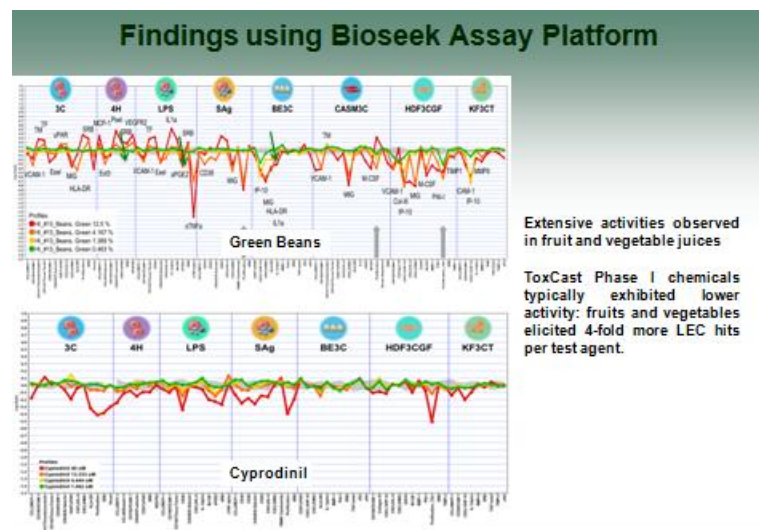


TOXCAST/TOX21 NEXT STEPS FOR INDUSTRY



- 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



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