

# Current State of the Science in Chemical Risk Assessment

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# *Outline*

- The Evolution of Regulatory Mandates & Implications for Risk Assessment
- Where are we?
  - The State of the Science in Risk Assessment
- Where do we Need to Go?
- Barriers/Constraints
- Conclusions/Recommendations

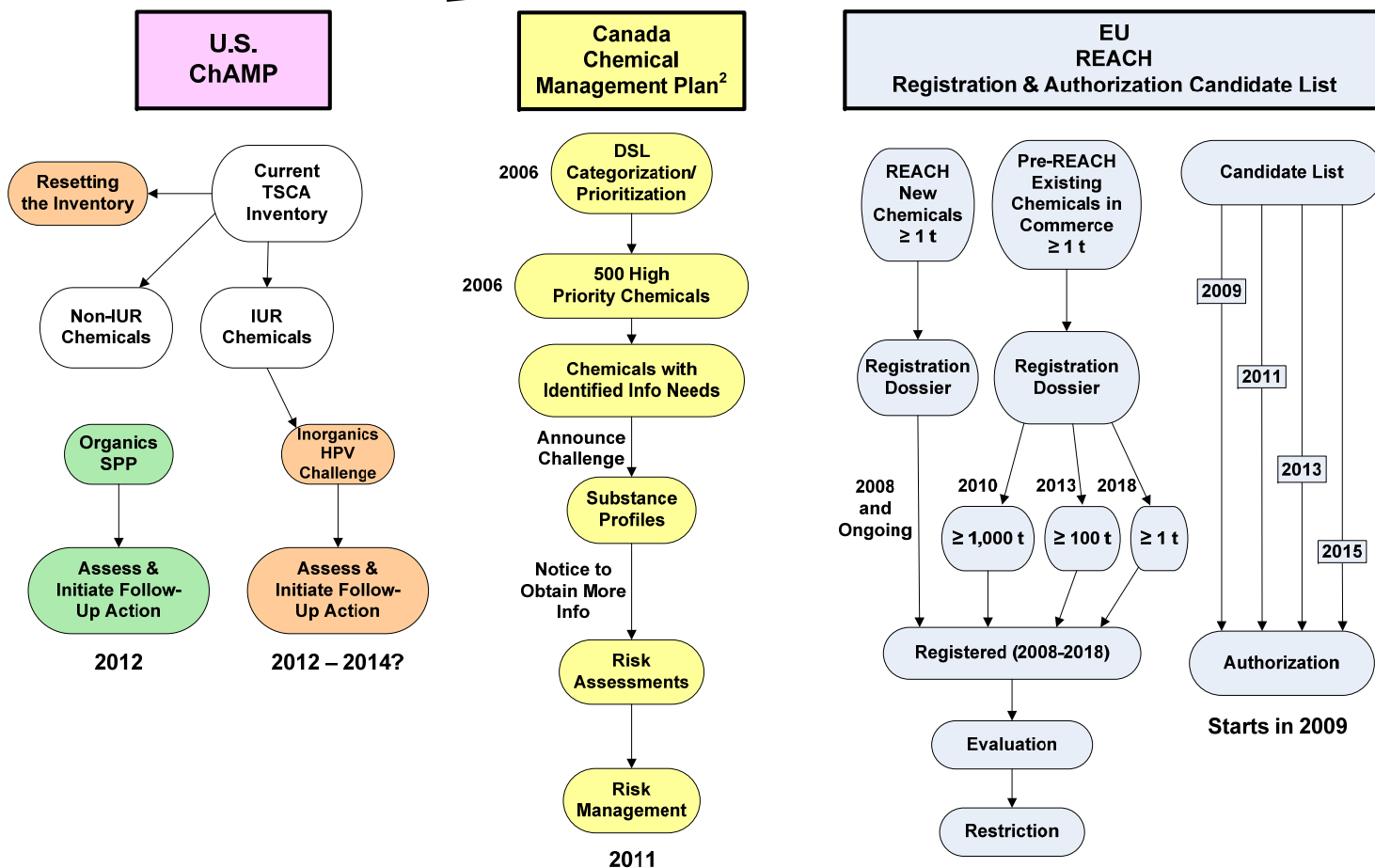
# ***Evolving Legislative Mandates for Industrial Chemicals***

- Chemicals in use at the time of introduction of modern chemicals legislation (late 1980's) were “grandfathered”
- Between the late 1980s and late 1990s, countries focussed assessments on approx. 100 out of the tens to hundreds of thousands of industrial chemicals in use (i.e., 0.1% to 1%)
- E.g., in Canada,
  - N= 44 on Priority Substances List (PSL) 1 by 1994;
  - N= 25 on PSL 2 by 2000
- Increasingly, legislation is requiring consideration of **all** chemicals
- Requires increased efficiency
  - much earlier consideration of mode of action as a basis to be predictive (e.g., computational modelling)
  - a risk assessment paradigm “shift”

# ***Evolving Legislative Mandates for Existing Chemicals (Cont'd)***

- Canada
  - “Categorization” (i.e., systematic priority setting) for 23, 000 chemicals by Sept., 2006 under the Canadian Environmental Protection Act (CEPA)
- Europe
  - Registration, Evaluation and Authorization of Chemicals (REACH) (2007)
    - Volume trigger and hazard based
    - Consistency between Existing and New Chemicals
    - Industry Responsibility
- U.S.
  - Voluntary Testing Initiatives (high volume)
  - Montebello Accord/ Chemical Assessment and Management Program (CHAMP) (moderate volume) 4

# Comparing U.S., Canada and EU Approaches

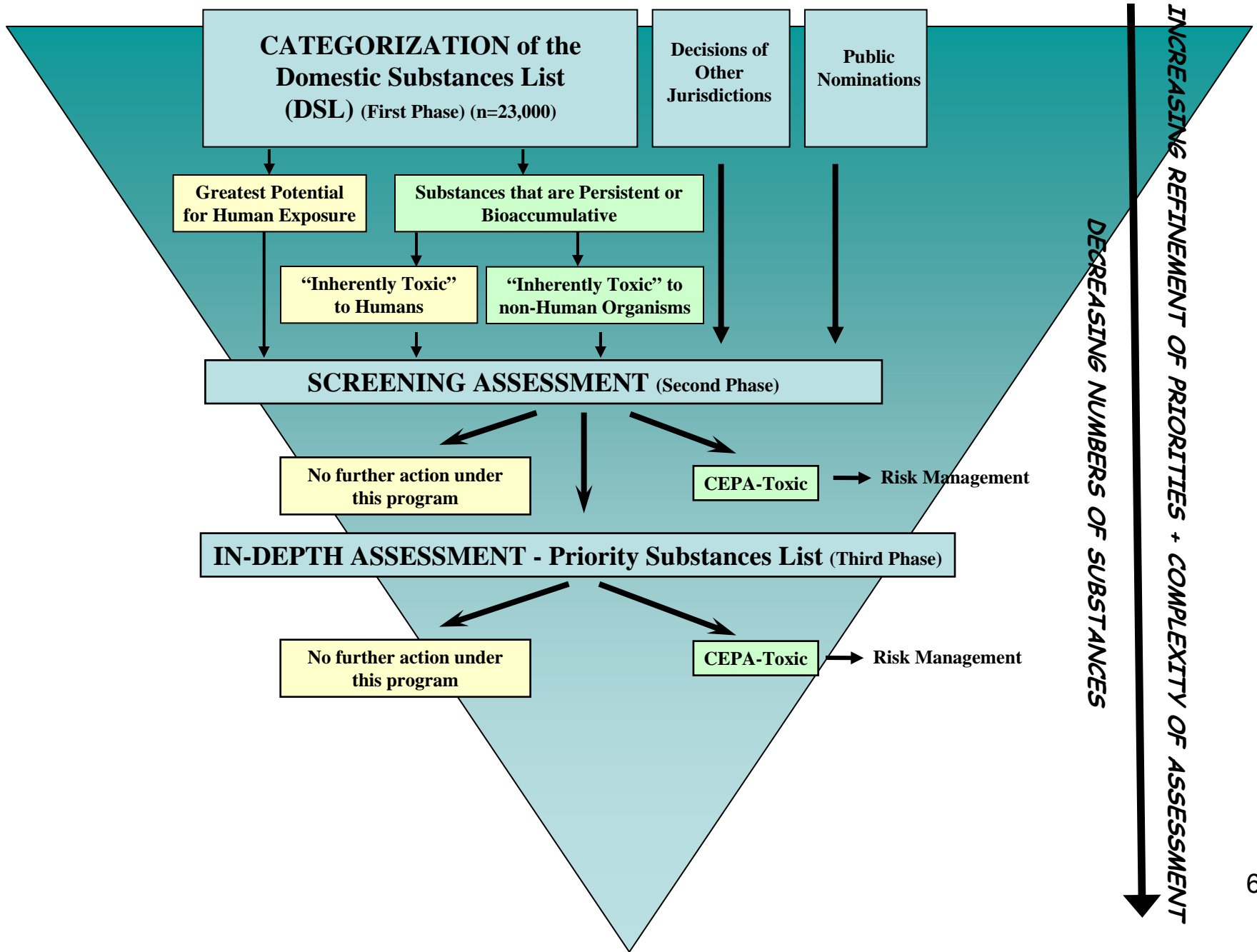


<sup>1</sup>DSL = Canadian Environmental Protection Act Domestic Substances List

<sup>2</sup>Other aspects of the CMP are not shown on this figure.

1,000 t = 2.2 M lbs.; 100 t = 220k lbs.; 1 t = 2.2k lbs.

# CEPA 1999 Existing Substances Program



# ***Simple and Complex Priority Setting Tools***

## EXPOSURE

Simple Exposure Tool (SimET) - Relative ranking of all DSL substances based on submitters (S), quantity (Q) and expert ranked use (ERU)

Complex Exposure Tool (ComET) - Quantitative plausible maximum age-specific estimates of environmental and consumer exposure for individuals based on use scenario (sentinel products), phys/chem properties & bioavailability

***Potential for exposure influential in setting priorities  
Included simple use profiling for all 23, 000 chemicals, more complex use  
profiling for priorities***

## HAZARD

Simple Hazard Tool (SimHaz) - Identification of high or low hazard compounds by various agencies based on weight of evidence and expert opinion/consensus

Complex Hazard Tool (ComHaz) - Hierarchical approach for multiple endpoints & data sources (e.g., (Q)SAR) including preliminary weight of evidence framework

# ***Post Categorization What's Changed?***

***Priorities*** not necessarily what we expected

- The value of a “risk-based” framework to consider ***all*** chemicals
  - Consumer vs. environmental exposure/profile
  - Volume ≠ exposure
  - Persistence/bioaccumulation ≠ exposure

***Integrated*** approach across compounds (less chemical-specific; more contextually relevant)

- Drawing to much greater extent on profiles of substances with similar uses, properties and hazards

# ***Post Categorization What's Changed? (cont'd)***

## ***Focus***

- Strategically targetting testing and “right sizing” risk management
- Only as much research/survey/assessment as is required to set a substance aside as a non-priority or to inform risk management
  - increasing efficiency
- Full assessments where required
  - Even for these few, early focus

# ***Post Categorization What's Changed (Cont'd)***

- ***Management*** (Chemicals Management Plan)
  - Less substance specific; more outcome focussed across chemicals
  - More industry responsibility
  - Early action being encouraged
    - Interventions tailored to evolving information base
  - Improved integration
    - CEPA as a driver to (a) determine the appropriate statute or jurisdiction to manage a risk, and (b) address the risk across media (air, food, water, products) and throughout the lifecycle
      - E.g., Food and Drugs and Hazardous Products Act

# ***Keep in Mind:***

- The appropriate performance indicator for such programs is ***not testing*** and ***assessment*** of chemicals, but rather:
- Effective and efficient ***management*** of risk
  - ***Now and in the immediate future***

# ***Learnings for Risk Assessment***

- Need for much broader focus
  - Maximize use of a much broader range of available data
    - Use profiling, predictive computational tools, previous assessments
  - Thinking to a much more significant extent in the context of “chemical space” rather than individual chemicals
- Need for ***much earlier assimilation*** in a ***risk assessment*** context
  - Hazard  $\neq$  risk
  - Toxicology  $\neq$  risk assessment
  - Exposure is often more discriminating than hazard

# *Principles of Good Assessment Practice*

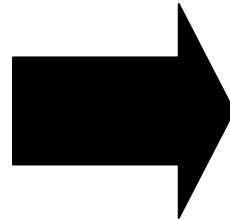
- *Early Issue Identification/Problem Formulation*
- *“Fit for Purpose” (&&&)*
- Inclusiveness
- Sound Science and Science Advice
- *Uncertainty* and Risk
- Transparency and Openness
- Review

# ***Risk***

## ***Assessment***

*(organizing & analyzing to set priorities & guide management  
(NAS/83 4-Step Paradigm)*

- hazard identification/  
characterization
- dose-response analyses
- exposure estimation
- risk characterization



# ***Risk***

## ***Management***

*(decision & action)*

- political
- social
- economic
- engineering

# ***Risk Assessment – Qualitative/Quantitative***

- Hazard Identification – potentially toxic?
  - Effects seen principally in animals (high doses, controlled conditions); sometimes in humans
- ***Hazard Characterization (qualitative – toxic to humans at relevant doses?)***
  - ***Based on some understanding of how it induces the effect***
- ***Dose Response Analyses (quantitative – how toxic?)***
  - Shape of the dose response curve
  - Range of observation ***& inference***
  - Quantitative ***relevance to humans***
- Exposure Estimation
- Risk Characterization

# ***“Default” in Risk Assessment***

- The vast majority of assessments are currently based on default assumptions
  - i.e., with no understanding of how the chemical induces effects
- Often, very few of the available data on toxicity/hazard directly contribute to dose-response analysis & risk characterization
  - Focus on the lowest effect level in the longest term study
- A function of:
  - how we conduct toxicity tests
  - limited progress in regulatory risk assessment
  - Lack of delineation of science judgment from science policy

# Default

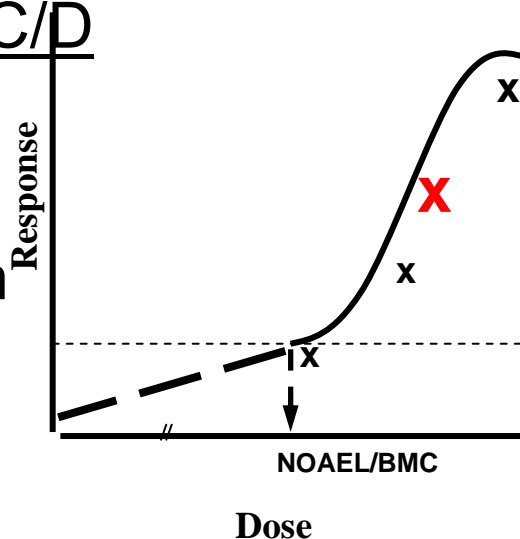


# Biologically (MoA) Based

- Curve fitting at high dose for point of departure for late (apical) endpoints
- Linear extrapolation or
- N/LO(A)EL or BMC/D  
UF
- Interspecies differences/human variability (x10)
- Missing endpoints



- More realistic doses
  - Characterizing relevant dose/response
- Earlier endpoints
- Interspecies differences/Human Variability
  - Kinetics/Dynamics



# ***Where Are We Trying to Go in A Risk Context?***

- Greater predictive power
- Higher relevance
  - Moving from default to more biologically based
    - Relevant pathways
    - Relevant doses
    - Relevant species

# ***The Continuum***

## ***Default ► Data-Informed***

- ***Default*** - *culpable neglect of some duty or obligation*
- **Database - Derived** - *databases of information, not group or chemical-specific*
- **Categorical** - *applies to categories of substances/species based on their characteristics (BSA correction; RFC - gases/particles)*
- **Chemical Specific Adjustment Factors** - *addressing kinetic or dynamic aspects with chemical specific or compound-related information*
- **Fully Data-Derived** – *biologically-based dose-response modelling addressing kinetic and dynamic aspects*

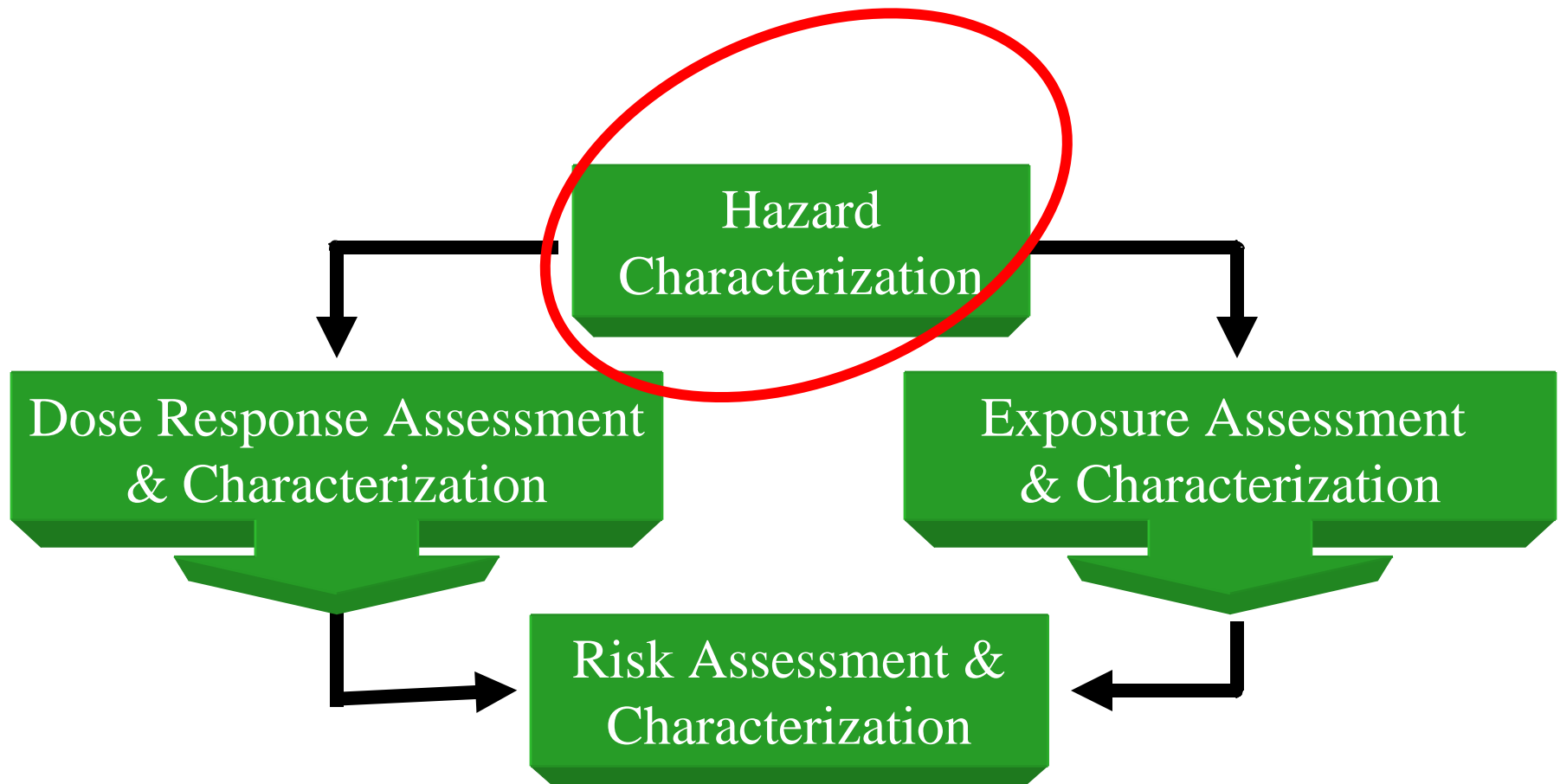
# ***Evolution of Toxicity Testing to Meet this Agenda***

- Paradigm shift away away from apical endpoints to perturbation of toxicity pathways
- More extensive use of computational toxicology and high throughput in vitro screening tests
- Broadest coverage of chemicals, end points, life stages
- Fewest animals; least suffering per animal
- Lowest cost; least time
- ***Detailed mechanistic and dose information for human health risk assessment***

# ***What's Required to Get the Risk Assessment Community There?***

- More assimilation in a mode of action and dose-response context at earlier stage
  - Relating less adverse early key events to traditional endpoints
  - Move from hazard id, where inordinate amounts of resources are currently invested in risk assessment
- Require ***justification of the use of default in an MOA context***
  - Reverse focus
- Increase understanding of the erroneous premise that default is always protective
  - Depends on how the chemical induces the relevant effect

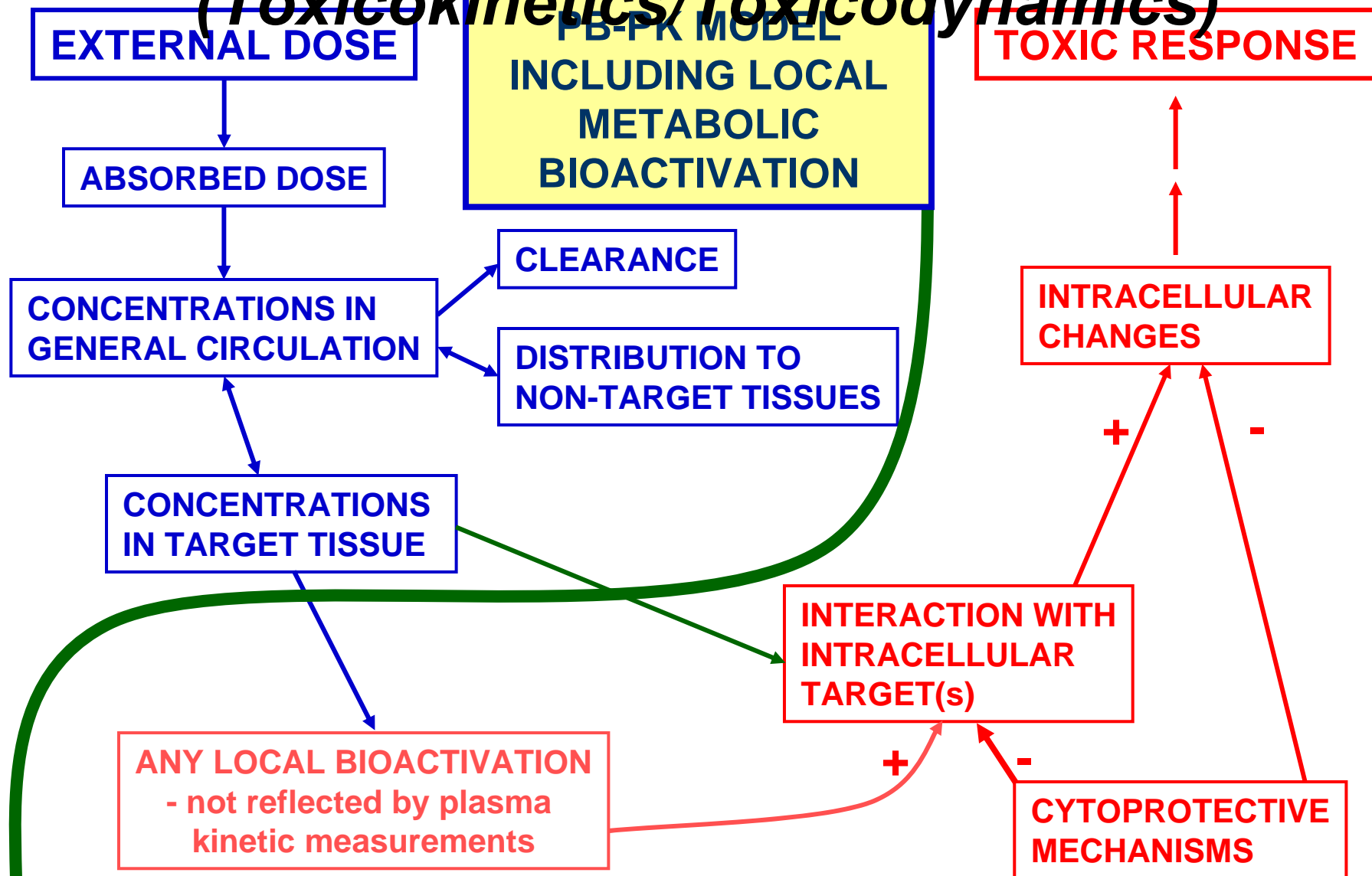
# *New and Improved NAS Paradigm*



Hazard Characterization = Weight of Evidence Analysis of Hazard and Information on **how** chemicals induce effects  
Toxic to humans at relevant doses?

# Mode of Action

## (Toxicokinetics/Toxicodynamics)



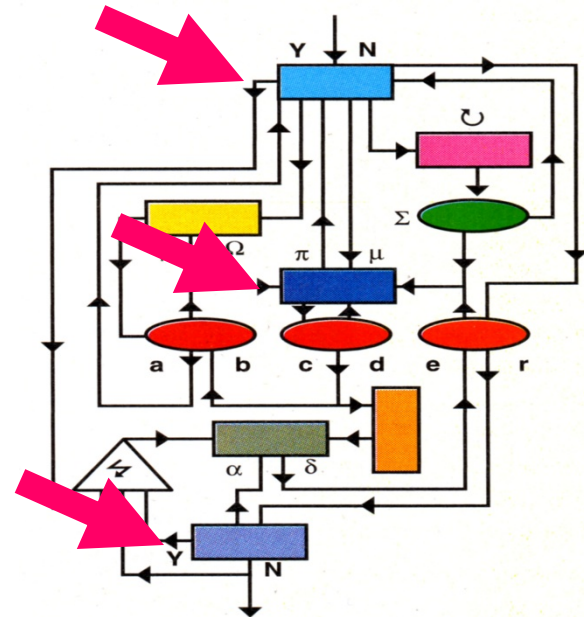
# Mode vs. Mechanism (Toxicokinetics/Toxicodynamics)

## Plausible Hypothesis

### Key event:

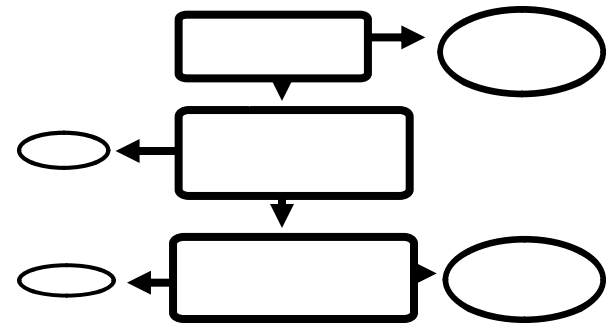
- Critical
- Can measure
- Repeatable

## Detailed Molecular Description



# ***What Helps in Considering Mode of Action and Human Relevance?***

- International Life Sciences Institute(ILSI)/International Programme on Chemical Safety (IPCS) Framework on Mode of Action/Human Relevance (MOA/HR)



# ***Focus on MOA***

## ***Increasing predictive capacity and utility of risk assessment***

- Drawing maximally and early on the most relevant information
  - data on kinetics/dynamics and the broader biology base
- Transparency
  - Rigor & consistency of documentation
  - Explicit separation of science judgment on weight of evidence from science policy considerations
- Doing the right research/testing
  - Iterative dialogue between risk assessors/researchers
  - Developing more progressive testing strategies

# ***How does the MOA/HR Framework Help in Transitioning the RA Community?***

## ***The ``Joiner``?***

- Enables us to relate testing results from high throughput technologies to traditional endpoints in a mode of action context
- Permits us to move away in informed fashion from hazard to more mode of action based predictive testing
- Effectively communicates this transition
- Need for understanding of the regulatory risk assessment community

# ***What's Preventing Getting There? Constraints in the Regulatory World***

- Performance indicator:
  - effective and efficient management of risk for large numbers of substances, **NOW**
- Simple (e.g., default) is easy to explain
- Science policy vs. science judgment
- Coordination of the science and regulatory communities
  - Training
  - Early engagement

# ***How Quickly does Risk Assessment Evolve?***

- In 1984, the “benchmark dose” was introduced
  - Now receiving widespread acceptance **25 yrs.** later
- Much guidance, many recommendations on analysis of uncertainty since the **1980's**
  - Several NAS & EPA reports
- Incorporation of PBPK modelling
  - Since the **early 1990's**
- Formal consideration of mode of action; chemical specific adjustment factors (National & International)
  - Since the **late 1990's**
- Tiered assessment (**'94 NAS report**)
- Problem formulation
  - EPA Guidance on Risk Characterization (**2000**)

# ***NAS Committee: Advancing Risk Assessment***

- Design of risk assessment
- Uncertainty and variability
- ***Selection and use of defaults***
- A unified ***default*** approach to dose-response
- Cumulative risk assessment
- ***Improving the utility of risk assessment***
  - ***Problem formulation***
- Stakeholder involvement
- ***Capacity building***

# *Recommendations*

- Drawing more robustly on existing data and developments
  - Importance of use profiling, exposure
- Engaging the regulatory risk assessment community, **now**
  - Determinants of the future of toxicity testing
  - Understand the pressures
  - Develop short term strategy for uptake
    - Mechanistic data/Default
      - Need for recognition of the competing science policy pressures to adopt “default” rather than more relevant and informative testing strategies

# *More Information*

- **U.S. EPA**

<http://www.epa.gov/NCEA/risk/guidance.htm>

- **Priority Setting/Iterative Assessment**

Existing Substances Division Website –

<http://www.hc-sc.gc.ca/exsd-dse>

- **ILSI RSI Website (MOA/HRF)**

<http://www.ilsi.org>

- **IPCS Harmonization Website  
(MOA/HRF/CSAF)**

<http://www.who.int/ipcs/methods/harmonization/index.html>