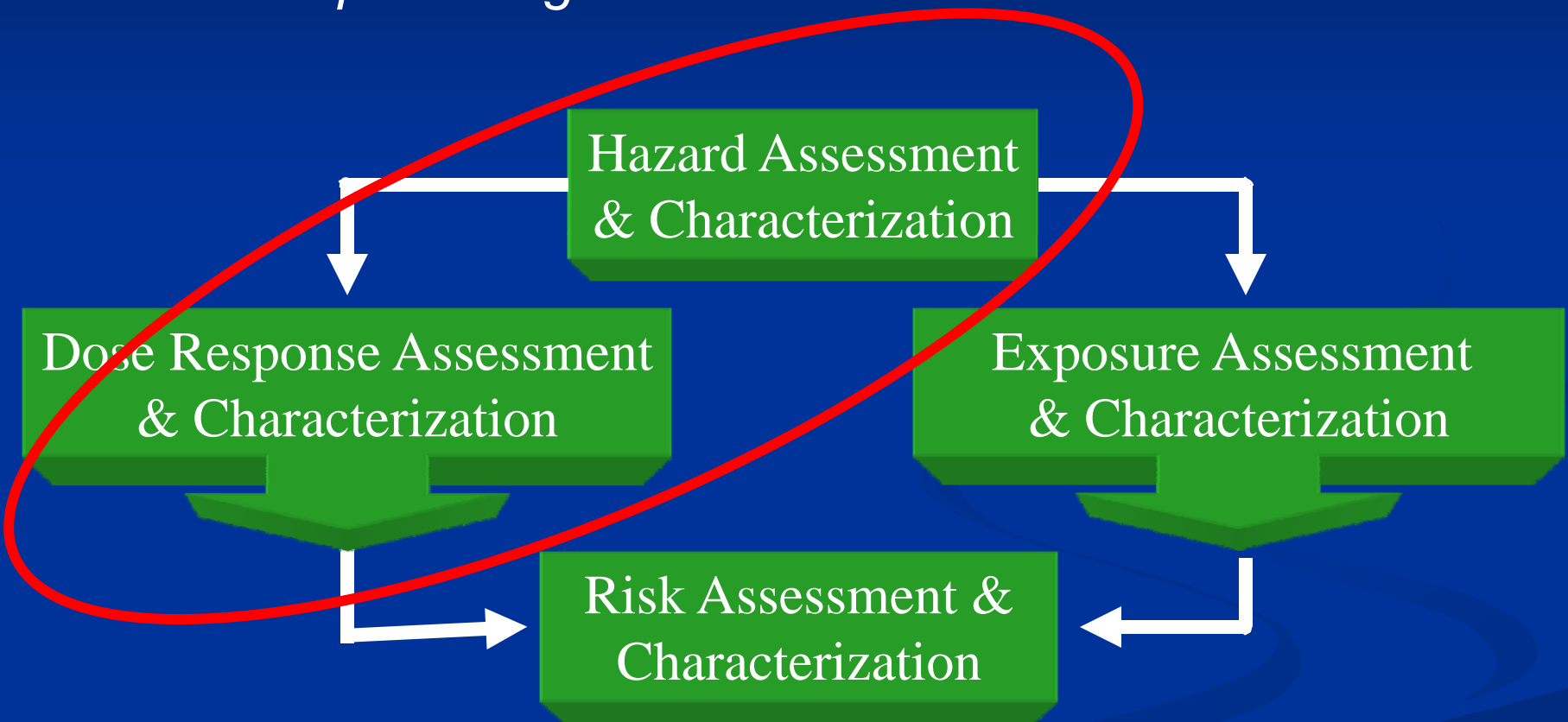


*Categorical Default Approaches to  
Uncertainty Factor Development in  
Chemical Risk Assessment*

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Cincinnati, OH

# *Where Does this Fit in Human Health Risk Assessment?*

*NAS 4-Step Paradigm*



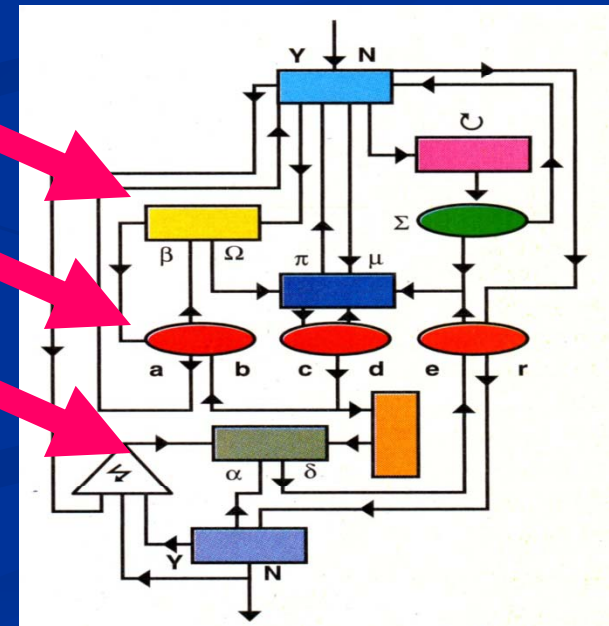
# Mode

Plausible  
Hypothesis with  
Measured Key  
Events

Key event:  
Critical  
Quantifiable

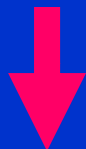
# Mechanism

Detailed  
Molecular  
Description  
of Causality

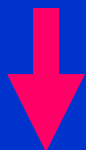


# MOA/HR (WOE) Framework

Q1. Is the weight of evidence sufficient to establish the MoA in animals?



Q2. Fundamental qualitative differences in key events?



Q3. Fundamental quantitative differences in key events?

Implications of Kinetic & Dynamic Data for Dose-Response

## *Default*

Reference/Acceptable/  
Tolerable Intakes

$$= \frac{N/LO(A)EL \text{ or } BMC/D}{UF}$$

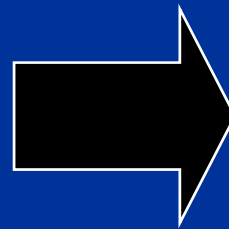
Uncertainty Factor

**Interspecies Differences**  
(x10)

**Human Variability**  
(x10)

**Adequacy of database**  
(x1-100)

## *Biologically (MoA) Based*



- Kinetics
- Dynamics

# *The Continuum*

## *Default ⇒ Data-Informed*

- Default - 10 x 10
- 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

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

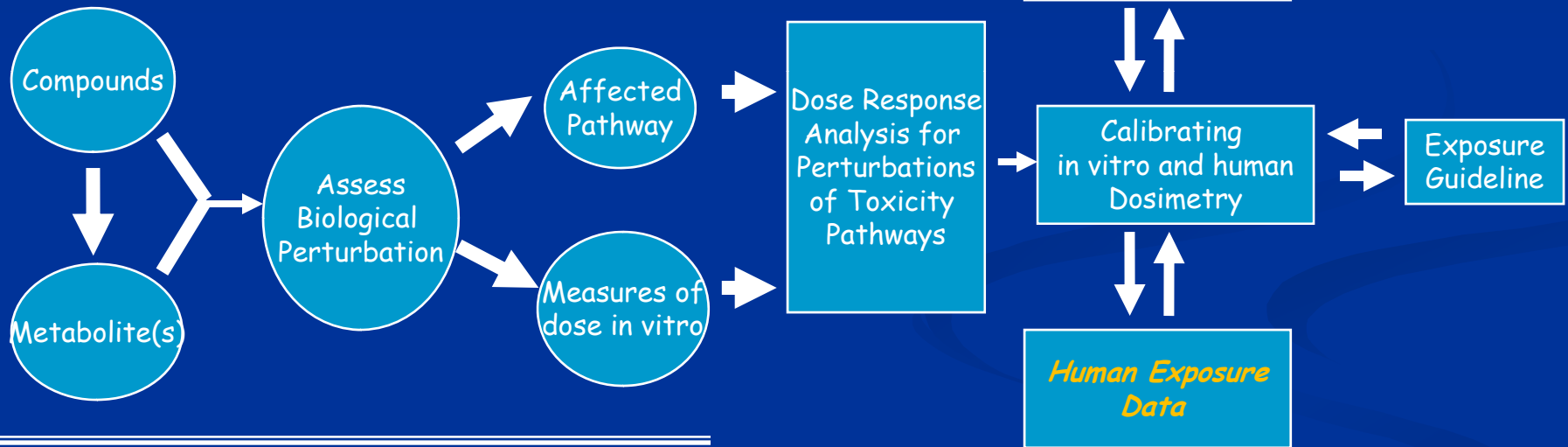
- Greater predictive power
- Higher relevance
  - Moving from default to more biologically based
    - Relevant pathways
    - Relevant doses
    - Relevant species

# U.S. NRC/NAS Toxicity Testing in the 21<sup>st</sup> Century

## Dose Response Assessment

### Chemical Characterization

### Mode of Action



### Hazard Characterization

### Exposure Assessment

### Risk Characterization

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