RISK21

Dose-Response Subteam:

Mode of Action Dose-Response (MOA-DR)

and

In Vitro to In Vivo Extrapolation (IVIVE)

Co-chairs:

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Ronald N. Hines, PhD

DOSE-RESPONSE SUBTEAM ROSTER

Global, Multi-Sector Stakeholder Representation

(n=40 scientists; 28 institutions represented)

Government (n=13; 5 agencies)

National Institutes of Health (NIDDKD)
Swiss Federal Office of Public Health
USDA (FSIS)
US EPA (NCEA, NHEERL, OPP, OW)
US FDA (CDER, CFSAN)

Academic (n=8; 7 institutions)

Auburn University
Imperial College London
Indiana University
Medical College of Wisconsin
University of Kansas
University of Nebraska Medical Center
University of Ottawa

Industry (n=11; 9 companies)

BASF
Bayer CropScience
Chevron Energy Technology Company
Dow Chemical Company
DuPont Haskell Laboratory
ExxonMobil Biomedical Sciences
Monsanto Company
Procter & Gamble Company
Syngenta

Non-profit (n=3; 2 institutions)

Hamner Institutes of Health Sciences
ILSI Research Foundation

Consultants (n=5; 5 companies)

Dose-Response Subteam Objectives

- Provide a forum to discuss approaches to dose extrapolation in human health risk assessment.
  - Address how an understanding of mode of action will influence low-dose extrapolation.
  - Build on the existing MOA / Human Relevance Framework (HRF) and Key Events Dose Response Framework (KEDRF) to quantitatively incorporate dose-response information.
- Address technical issues regarding *in vitro* to *in vivo* extrapolation.

Human Relevance, MOA, and Dose Response: Evolution of the Frameworks

Original IPCS MOA framework
Sonich-Mullin et al., *Regul Toxicol Pharmacol* 34:146-152, **2001**.

ILSI human relevance framework for cancer
Meek et al., *Crit Rev Toxicol* 33:591-653, **2003**.

Extending the human relevance framework to include genotoxic carcinogens and non-carcinogens
Seed et al., *Crit Rev Toxicol* 35:664-672, **2005**.

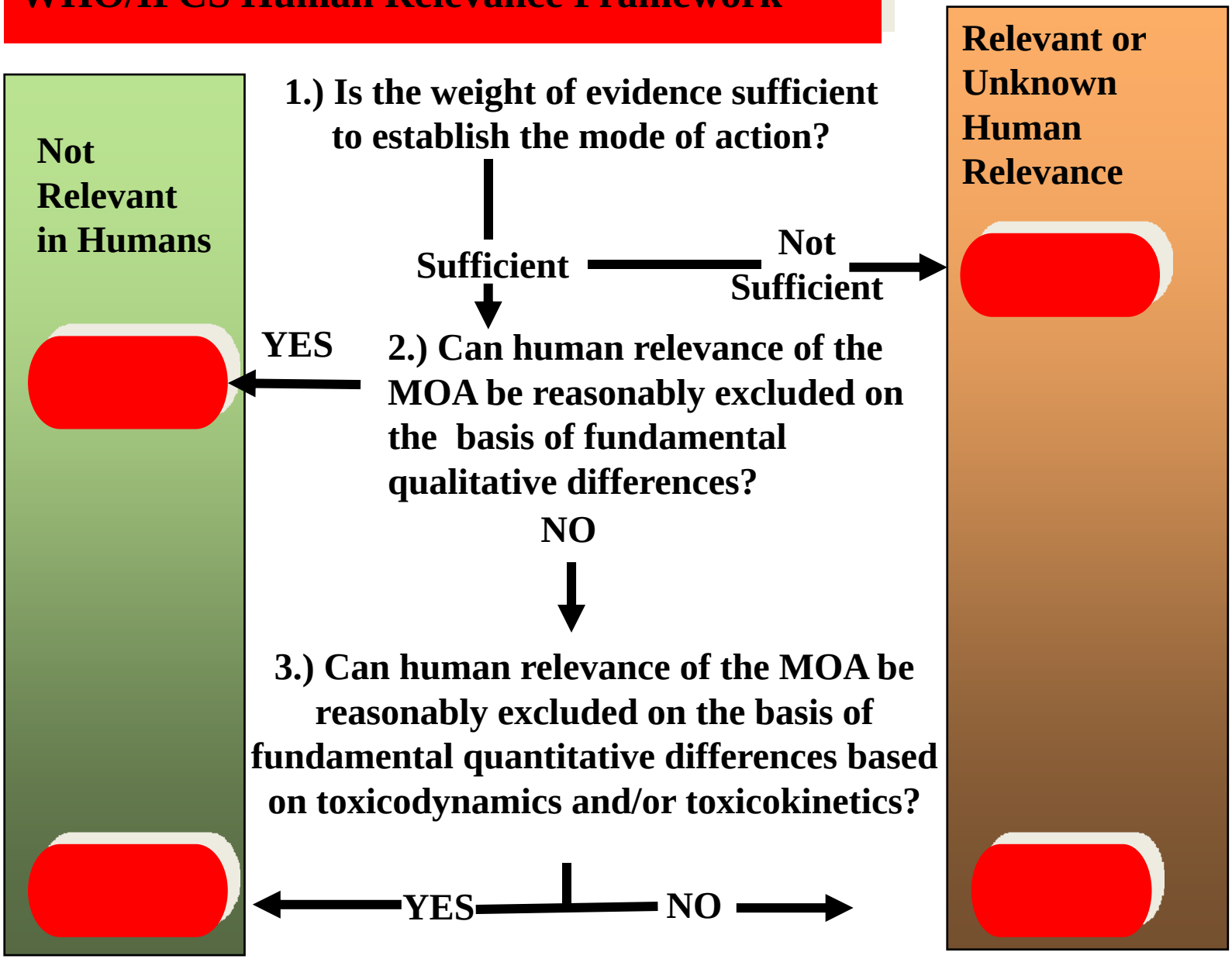
IPCS form of human relevance framework for cancer
Boobis et al., *Crit Rev Toxicol* 36:781-792, **2006**.

IPCS human relevance framework, including non-cancer
Boobis et al., *Crit Rev Toxicol* 38:87-96, **2008**.

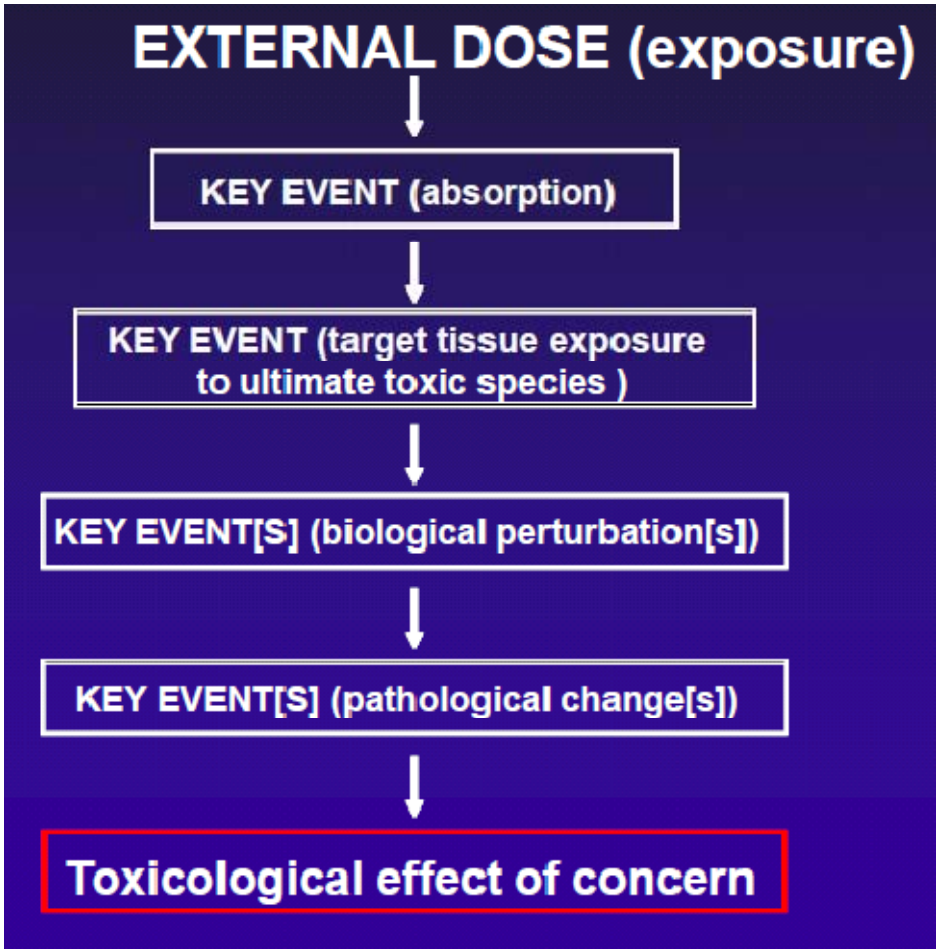
Key events dose-response framework
Julien et al., *Crit Rev Fd Sci Nutr* 49:682-689, **2009**.

CURRENT PROJECT WILL DEVELOP METHODOLOGY FOR QUANTITATIVE ASSESSMENT OF KEY EVENTS DOSE-RESPONSE FOR RISK ASSESSMENT MODELING.

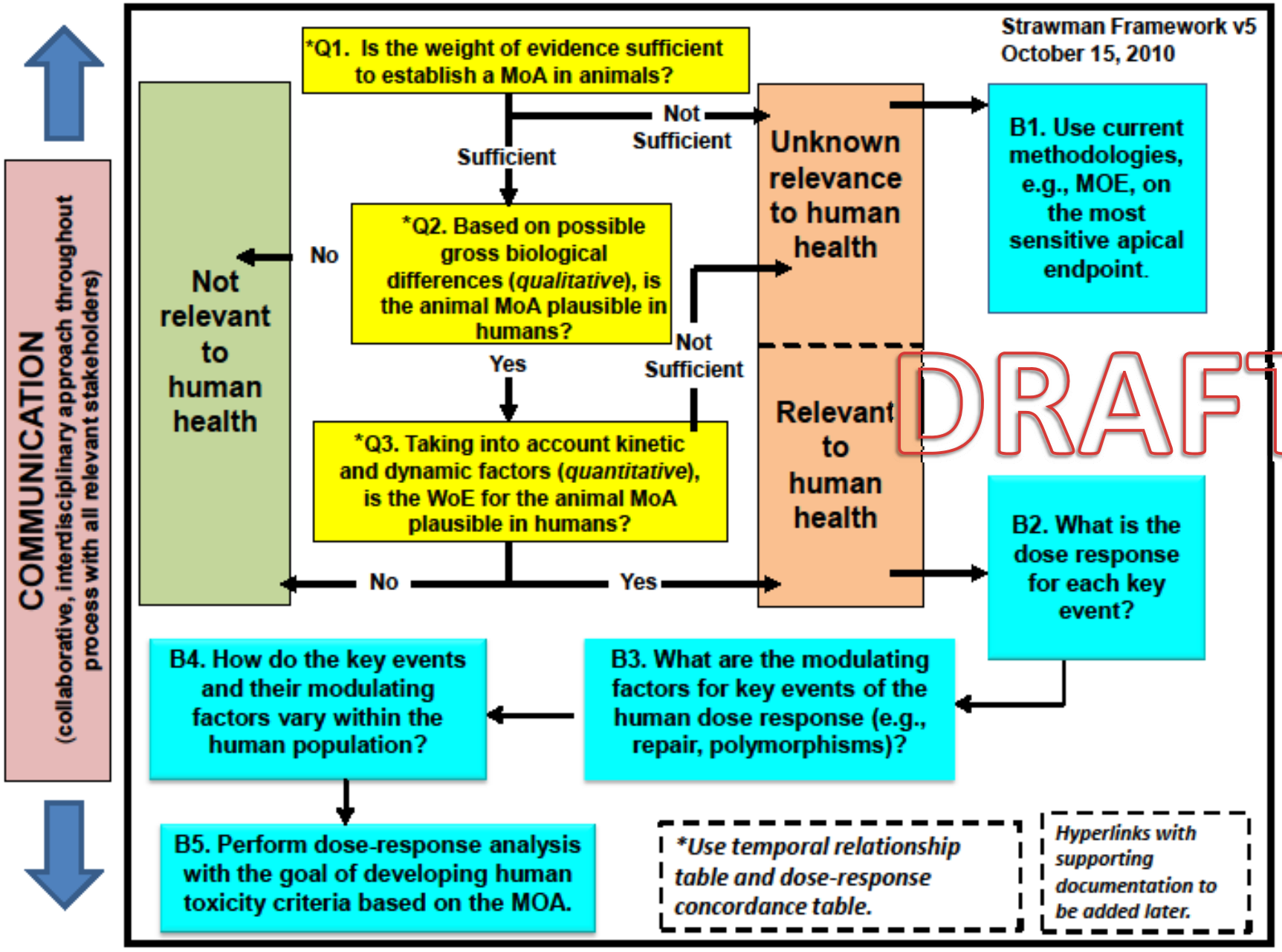
WHO/IPCS Human Relevance Framework



Key Events Dose Response Framework



Julian et al., *Crit Rev Food Sci Nutr* 49:682–689, 2009.


Strawman Framework v5
October 15, 2010
COMMUNICATION
(collaborative, interdisciplinary approach throughout process with all relevant stakeholders)
*Q1. Is the weight of evidence sufficient to establish a MoA in animals?
Not Sufficient
Sufficient
Unknown relevance to human health
B1. Use current methodologies, e.g., MOE, on the most sensitive apical endpoint.
*Q2. Based on possible gross biological differences (qualitative), is the animal MoA plausible in humans?
No
Not relevant to human health
Not Sufficient
Yes
*Q3. Taking into account kinetic and dynamic factors (quantitative), is the WoE for the animal MoA plausible in humans?
No
Yes
Relevant to human health
B2. What is the dose response for each key event?
B3. What are the modulating factors for key events of the human dose response (e.g., repair, polymorphisms)?
B4. How do the key events and their modulating factors vary within the human population?
B5. Perform dose-response analysis with the goal of developing human toxicity criteria based on the MOA.
*Use temporal relationship table and dose-response concordance table.
Hyperlinks with supporting documentation to be added later.
DRAFT

Work Group Formation

PURPOSE: To develop supporting documentation for each of the blue boxes in the draft Framework

WG1: Use current methodologies, e.g., MOE, on the most sensitive apical endpoint

Leader: Kerry Dearfield

WG2: What is the dose response for each key event?

Leader: Ted Simon

WG3: What are the modulating factors for key events of the human dose response (e.g., repair, polymorphisms)?

Co-leaders: Sam Cohen, Jim Klaunig

WG4: How do the key events and their modulating factors vary within the human population?

Leader: Julian Preston

DRAFT Dose-Response Concordance Table (v5)

DRAFT

- Will inform the choice of which key event is appropriate to choose as the basis of the DR assessment.
- Where possible, show actual DR curves.
- When not possible, provide narrative.
- It may be helpful to have the same x-axis dose in all graphs so the relationship between the key events can be seen, e.g., Fig. 1 in Simon et al. (2009).

APICAL EVENT	QUALITATIVE CONCORDANCE			QUANTITATIVE CONCORDANCE	QUANTITATIVE DOSE RESPONSE	
	Animals	Humans	Strength	Humans	Animals	Humans
Key event						
Associative event						
Modulating event						

- Will determine which key event is most relevant to humans.
- Will support statements about the relevance of the animal MOA to humans.
- Endpoint(s) are not included if WoE deems them irrelevant to humans.

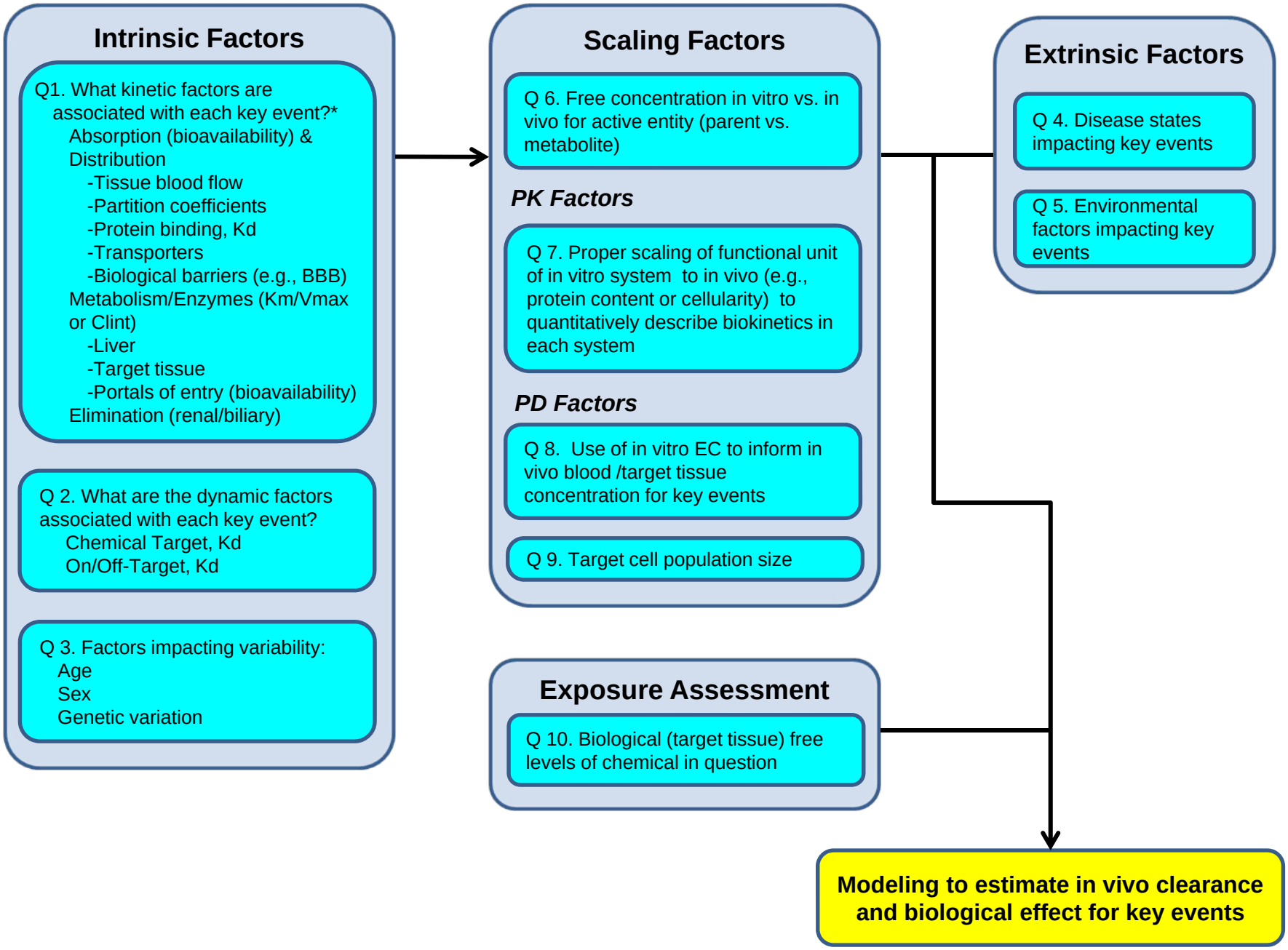
- Will inform animal-to-human extrapolation.
- Should contain information on EC50 and/or POD values and likely other quantitative measures in both humans and animals.
- Also a place to include NOAELs or other measures of threshold, e.g., projection from EC05 (Silkworth et al., 2005) or "hockey-stick" (Lutz and Lutz, 2009).

Dose-Response: Testing the Updated Framework

- **Case study criteria for testing the framework**
  - Relevant to humans (data-rich)
    - based on exposure
    - exposure not relevant
  - Not relevant to humans
  - Unknown relevance
    - data-poor
    - data-rich
- **Sources, leverage as much as possible**
  - Published case studies
  - Nuclear Receptor Mode of Action Workshop (AHR, CAR/PXR, PPARα)
  - ARA Beyond Science and Decisions workshop case studies
  - New case studies

IVIVE Working Group

- Workgroup formed late Fall, 2010
- Utilization of PB/PK and PD modeling to predict response based on dose-dependent MoA and exposure assessment
- Work to date
  - Draft assumptions
  - Begun formulating critical knowledge gaps
  - Identification of key data necessary for modeling


Intrinsic Factors
Q1. What kinetic factors are associated with each key event?*
Absorption (bioavailability) & Distribution
-Tissue blood flow
-Partition coefficients
-Protein binding, Kd
-Transporters
-Biological barriers (e.g., BBB)
Metabolism/Enzymes (Km/Vmax or Clint)
-Liver
-Target tissue
-Portals of entry (bioavailability)
Elimination (renal/biliary)
Q 2. What are the dynamic factors associated with each key event?
Chemical Target, Kd
On/Off-Target, Kd
Q 3. Factors impacting variability:
Age
Sex
Genetic variation
Scaling Factors
Q 6. Free concentration in vitro vs. in vivo for active entity (parent vs. metabolite)
PK Factors
Q 7. Proper scaling of functional unit of in vitro system to in vivo (e.g., protein content or cellularity) to quantitatively describe biokinetics in each system
PD Factors
Q 8. Use of in vitro EC to inform in vivo blood /target tissue concentration for key events
Q 9. Target cell population size
Extrinsic Factors
Q 4. Disease states impacting key events
Q 5. Environmental factors impacting key events
Exposure Assessment
Q 10. Biological (target tissue) free levels of chemical in question
Modeling to estimate in vivo clearance and biological effect for key events

Next Steps

- **2011**
  - Focused work effort
    - Framework: Work Groups to continue developing supporting documentation for framework
    - IVIVE Work Group
    - Case study development (n = ~6)
  - Presentations at scientific meetings (e.g., ARA Beyond Science and Decisions)
- **2012**
  - Presentations at scientific meetings (e.g., SOT, SRA, HESI, others)
  - Publications