

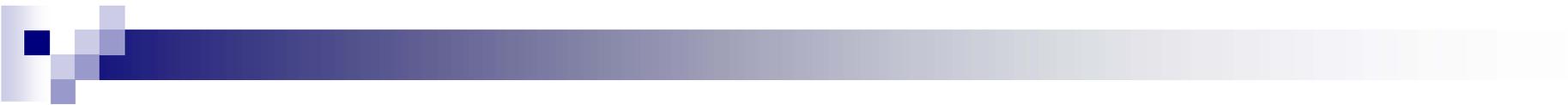
The Evolving Concept of Susceptibility in Risk Assessment

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Outline

1. What is susceptibility (S)?
2. Where is S addressed in risk assessment (RA)?
 - Chemical
 - Microbial
3. How is S addressed in RA?
4. What are the S issues in RA?
5. Conclusions



1. What is Susceptibility?

Many discipline-based variations, emphases

- Ecology: organism level, sensitive to poison
- Medicine: host physiology, individual scale
- Epidemiology: intrinsic and acquired host traits, dysfunction relative to other individuals or populations
- Toxicology: probability and extent of response conditional on exposure, population scale, sensitive or vulnerable



But ...

All definitions of susceptibility include 3 components

- Physiological state of the host
- Relational construct between the host and an external agent
- Change in the host resulting from contact with the agent
 - Change is usually, but not always, adverse



Fostering Confusion

- Susceptibility is used interchangeably with other terms
 - Sensitive
 - Vulnerable
- However, there are definitional differences that matter



Susceptibility vs. Sensitivity

Susceptibility is:

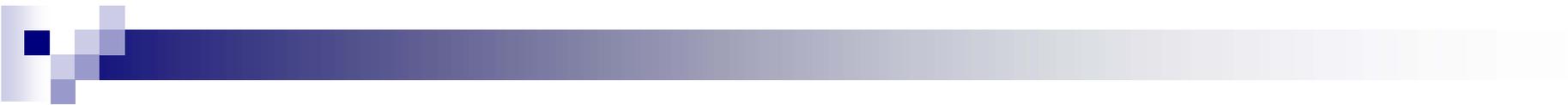
A capacity leading to higher risk

at a given exposure level, due to biological (intrinsic) factors that can modify the effect of a specific exposure

Sensitivity is:

A capacity for higher risk

due to the **combined** effect of susceptibility (biological factors) **and** differences in exposure



Vulnerability

- Definitions focus on the capacity to be *harmed or injured*
- WHO attributes vulnerability (V) to *both*
 - Intrinsic (biological) factors and
 - Extrinsic (environmental, behavioral) factorsAnd states that V is S + environmental and behavioral factors

However, no formal definition for RA



Susceptibility vs. Vulnerability

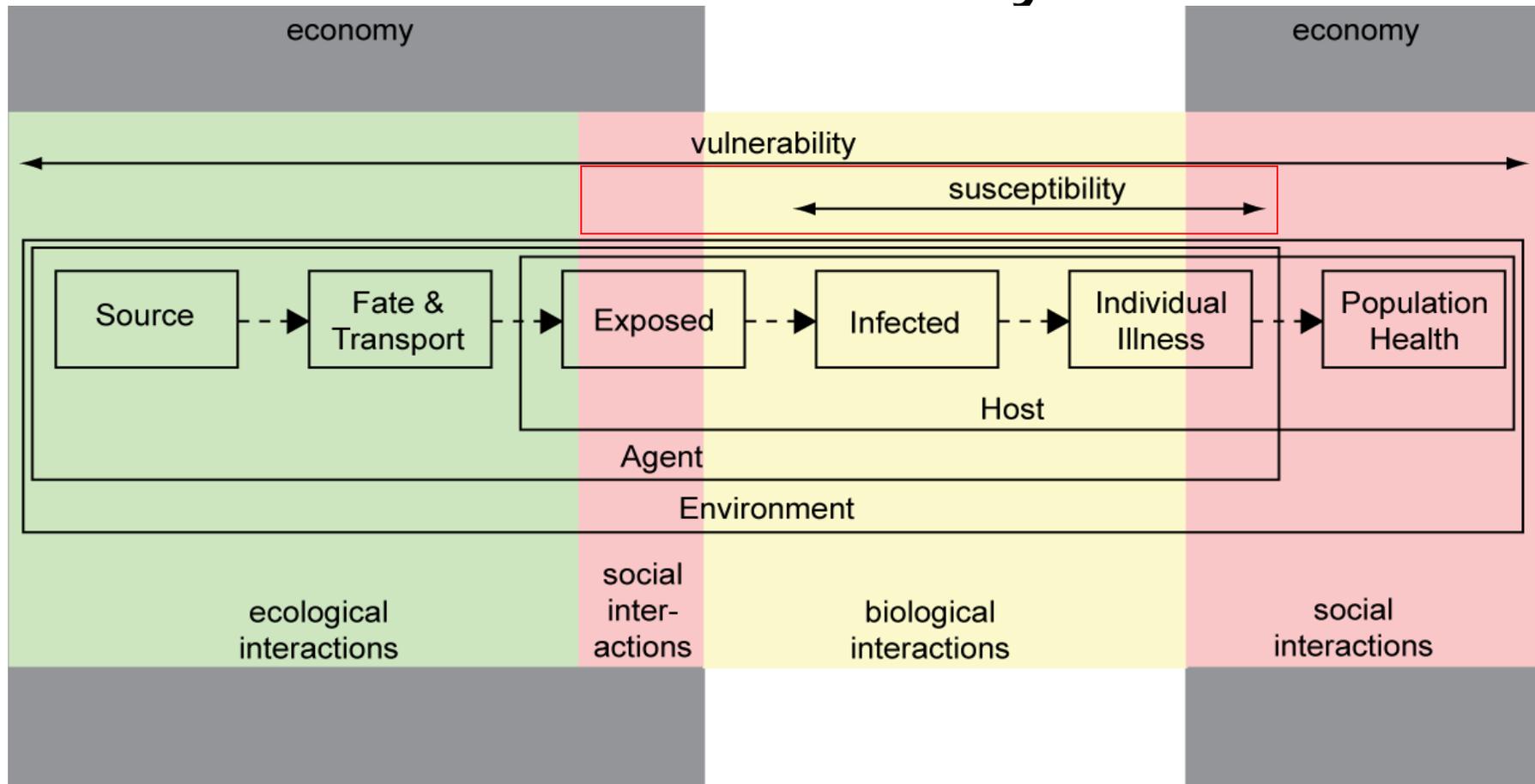
Susceptibility

- Includes intrinsic factors only
- Characteristic of an individual
- Defined by the host

Vulnerability

- Includes intrinsic *and extrinsic* factors
- Characteristic of an individual *or a group*
- Defined by the host (*behavior*) *and environment*

Susceptibility is Part of Vulnerability



Modified from de Roda Husman, 2008



Key Conceptual Issues in Framing Susceptibility for RA

- Individual vs. population scale
- Intrinsic and/or extrinsic factors
 - Intrinsic *and exposure pathway* (behavior) affect host's probability and severity of response (Embrey et al, 2003)
- Rely on host descriptors



2. Where is Susceptibility Addressed in RA?

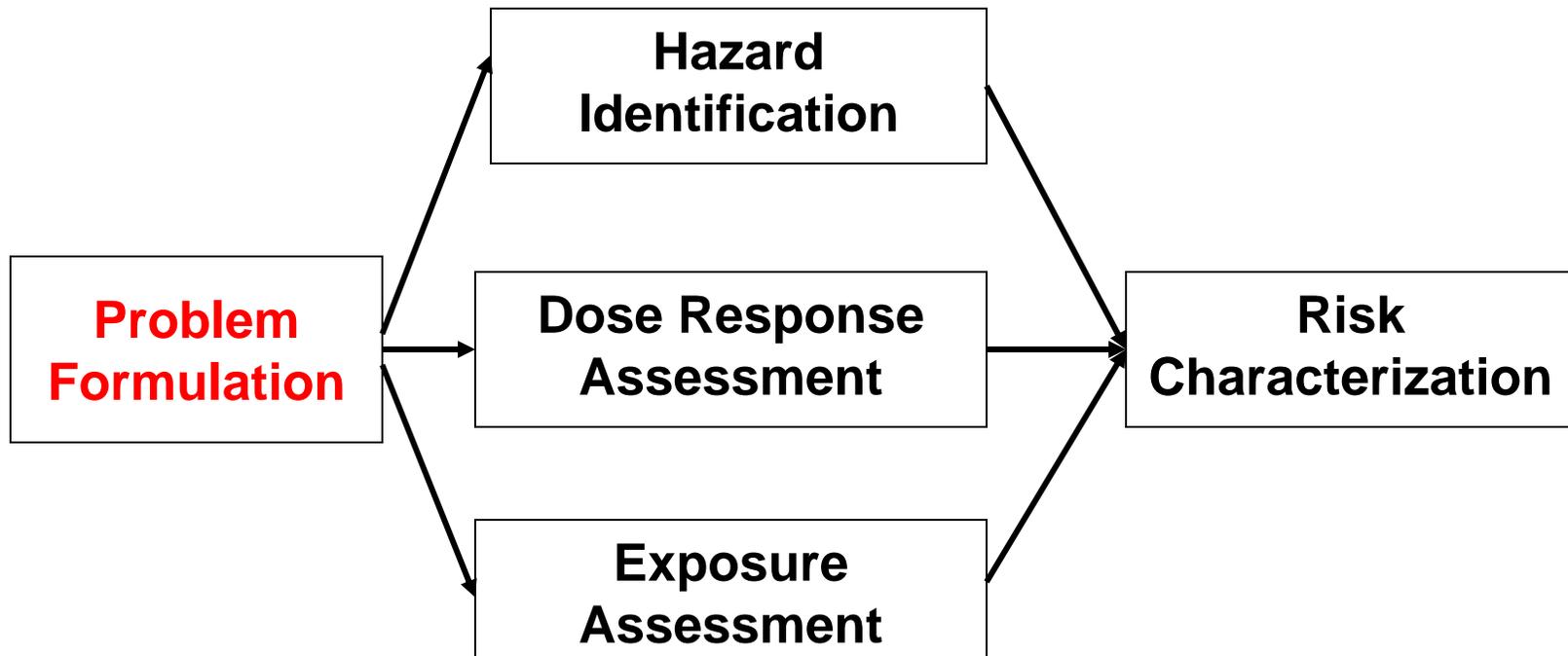
- Typically in the **Dose-Response (D-R)** step of RA
- Emphasis is on **host characteristics**
 - Usually these characteristics are not explicitly linked to susceptibility
 - Sometimes host-agent relationship traits are noted



3. How is Susceptibility Addressed in RA?

- **Lists of subpopulations** based on observable characteristics
 - May be mandated in laws, regulations
 - E.g., children, pregnant women, elderly
- Different human health **outcomes** &/or **severity** based on the literature
 - E.g., More severe *Cryptosporidiosis* among the immune-compromised individuals
- Separate **D-R curves** are sometimes used

FDA's RA Framework

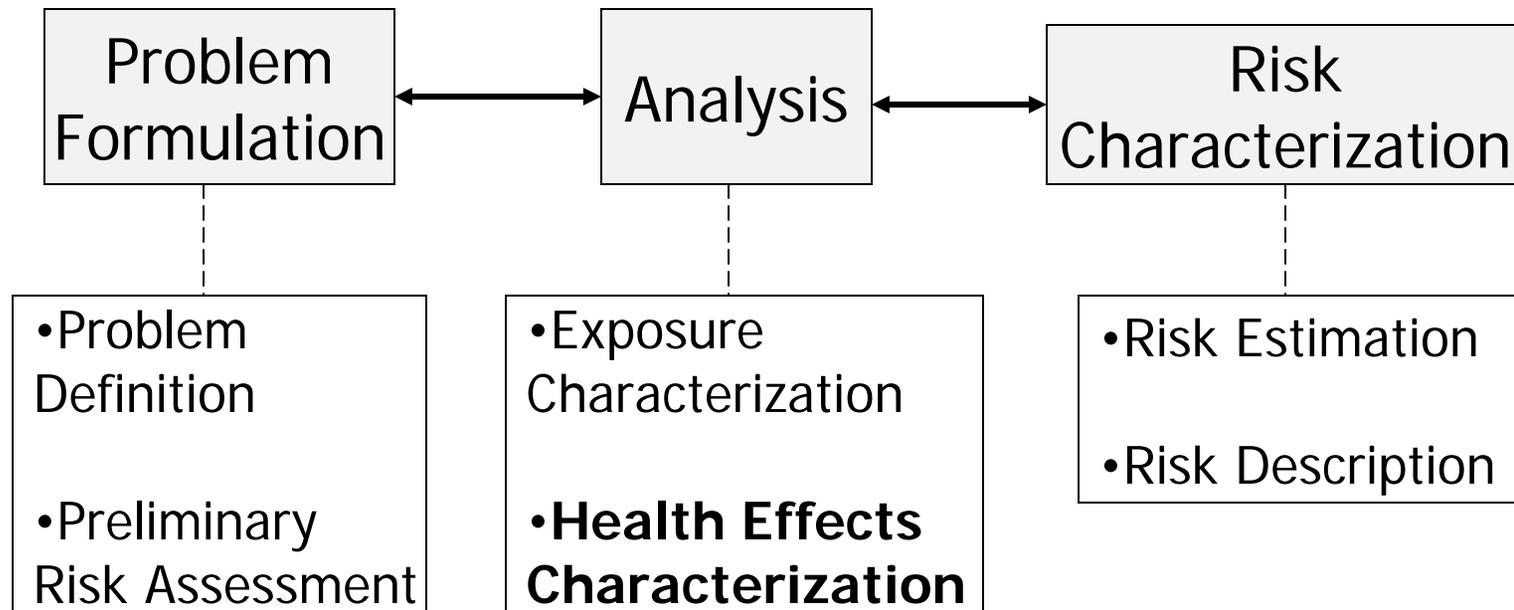


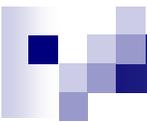


How is Susceptibility Handled in the FDA Framework?

- Primarily in the **Dose-Response** (Hazard Characterization) step
 - Subpopulations are modeled separately
 - Dose-response curves are developed for each group based on animal and human data
 - Distributions are adjusted for variability in host susceptibility
- **Distributions are combined** in Risk Characterization to create a **probabilistic** estimate for the entire population

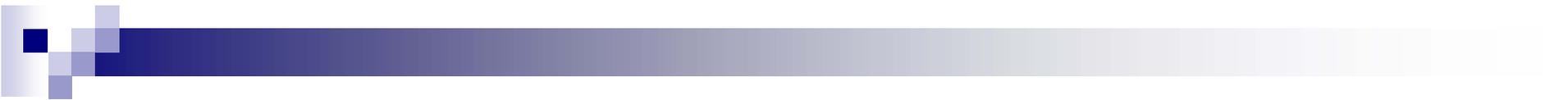
ILSI's Microbial RA Framework





How is Susceptibility Addressed in the ILSI Framework?

- Susceptibility is not highlighted as a key issue
- Primarily appears in the **Dose-Response step** within Health Effects Characterization
- Emphasis is on **host characteristics**
 - Other elements related to the pathogen and the host-pathogen relationship are in other components of the paradigm
 - These are not explicitly linked to susceptibility



Ex.: Addressing Susceptibility

Analysis of 9 food-borne microbial pathogen RAs that included S (all in the D-R step)

■ Explicit decisions

- Age groups as S subgroups: 5 of 9 MRAs
- More severe outcomes in S subgroups: 4 of 9
- No differences in S *within* subgroups: 2 of 9

■ Implicit assumptions

- No impacts of gender or genetic differences
- No differences in S *within* subgroups



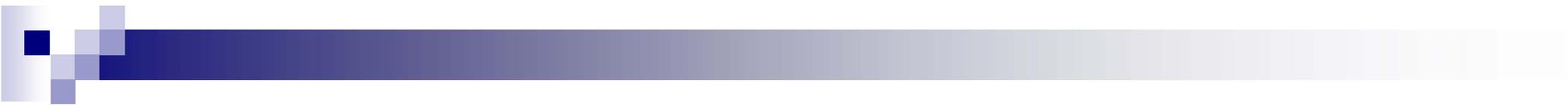
But...

- Only 1 MRA explicitly defined susceptibility
 - Host capacity to defend against the pathogen
- 5 of the 9 MRAs addressed susceptibility in all steps of the RA
 - Mostly by using recognizable subgroups



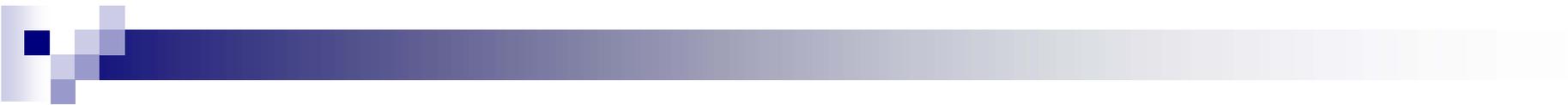
4. What are the Susceptibility Issues in RA?

- Susceptibility is a complex concept
 - Can we agree on 1 conceptual definition for RA?
 - How explicitly can S be defined for a RA?
 - Agent, host (scale), outcome/s, severity
 - Available knowledge and data
 - Can it be used comprehensively & systematically in RA?
- Not always fully addressed in all RA steps
 - Is the conceptual base incomplete, vague?



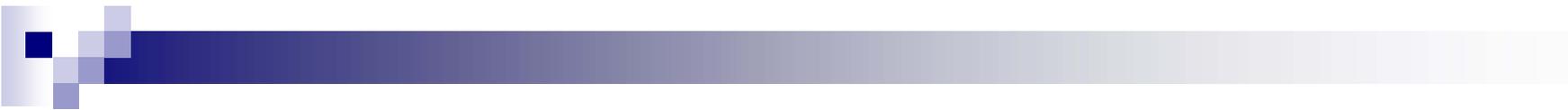
What is the Scope of Susceptibility?

- Population as a whole or subpopulations?
 - How should variability be handled within either choice?
- Specific location?
 - Region as general population reference point?
- Specific outcome/s?
 - Acute, chronic, sequelae?
 - Differential outcomes and/or severity?



From Susceptibility Concept to Analytic Approach

- What are the key factors (source to effects)?
 - Relationships between them?
 - Can they be diagrammed?
 - Are there differential exposure pathways, probabilities?
- Are there sufficient data to translate the conceptual model into a complete analytic model for S?
 - What are the gaps in knowledge, data?
 - What assumptions, defaults are needed?
 - Separate dose-response curves desirable and feasible?



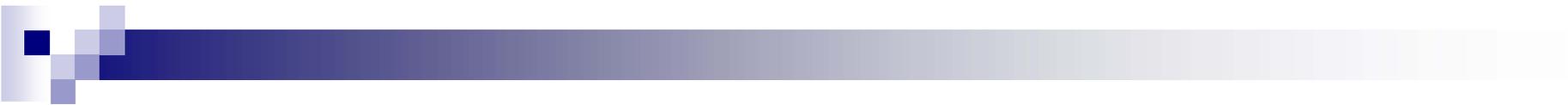
Evaluate the Susceptibility Results

- What impacts did the design choices have?
 - How did the data quality affect the susceptibility results?
 - How did the assumptions and defaults affect the susceptibility conclusions?
- Were the key sources of uncertainty and variability identified for S subgroups?
- Were the susceptibility issues in the problem statement adequately addressed?



Recommendations

- Explicitly define susceptibility in the problem formulation and add S decisions to RA scope
- Draft a comprehensive conceptual diagram to
 - Place the S concept throughout the RA steps
 - Organize available data and evaluate data quality
 - Identify gaps in knowledge and evidence
 - Determine needed assumptions and defaults
 - Design an operational analytic approach
- Evaluate and explicitly link the S results back to the problem statement



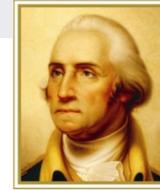
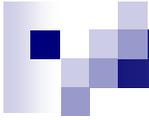
5. Conclusions

So where are we with the concept of susceptibility?

- Still evolving – stay tuned!
- Definitions for specific RAs will always differ
 - Legal mandates
 - Available data and analytic feasibility

However,

Consensus about the concept for use in RA would improve communication across disciplines.



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Thank You!