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

Parkin and Balbus, 2000
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

Balbus and Parkin, 2000
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

Makri et al, 2004
Vulnerability

- Definitions focus on the capacity to be *harmed or injured*

- WHO attributes vulnerability (V) to *both*
  - Intrinsic (biological) factors and
  - Extrinsic (environmental, behavioral) factors

  And states that V is S + environmental and behavioral factors

However, no formal definition for RA

WHO Guidance, 2010 pending
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

WHO, 2010 pending
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

- Hazard Identification
- Dose Response Assessment
- Exposure Assessment
- Risk Characterization
- Problem Formulation

Modified NRC, 1983
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

- **Problem Formulation**
  - Problem Definition
  - Preliminary Risk Assessment

- **Analysis**
  - Exposure Characterization
  - Health Effects Characterization

- **Risk Characterization**
  - Risk Estimation
  - Risk Description
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

Parkin, 2008
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.
Thank You!