

**EPA**  
United States  
Environmental Protection  
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## Challenges in Dose-Response Assessment

Jeff Swartout,  
U.S. EPA/ORD/NCEA

Office of Research and Development  
National Center for Environmental Assessment

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## Road Map

- Dose response modeling
  - issues
  - infection
  - illness
- Sensitive subpopulations
- Use of surrogates
- Future directions

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## Dose-Response Assessment: General Approach

- Determining the relationship between the dose of a pathogen and the incidence of infection or specific adverse health effects in an exposed population.
- Response probability determined by fitting a mathematical model to dose-response data
- One-hit theory applies
  - Each organism capable of surviving host defenses to initiate an infection
  - Non-zero probability no matter how low
  - Thresholds?

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## Dose-Response Assessment: Exposure Media Issues

- Key issues are different for different exposure scenarios
  - Food exposure or person-to-person contact
    - high-dose occasional exposures (buffered?)
    - risks usually in the range of the data
  - Drinking water exposure
    - low-dose frequent exposures (un-buffered)
    - need extrapolated unit-risk measures

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## Data Requirements (?)

- Need response data for:
  - a specific effect from
  - a specific pathogen administered to
  - a specific host by
  - a specific route under
  - specific conditions
- Need both low- and high-response data (“response anchoring”)

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## Dose-Response Models: functional forms

**Exponential**  
 $Pr = f(d) = 1 - e^{-rd}$   
 d = dose; r = unit infectivity

**beta-Poisson (beta-exponential)**  
 $Pr = f(d) = 1 - {}_1F_1(\alpha, \beta - \alpha, -d)$   
 ${}_1F_1$  = confluent hypergeometric function  
 $\alpha, \beta$  = beta distribution parameters  
 unit infectivity ( $r$ ) =  $\alpha \div (\alpha + \beta)$

**Plateau model**  
 $Pr = (1 - fr) \times f(d)$   
 fr = immune fraction

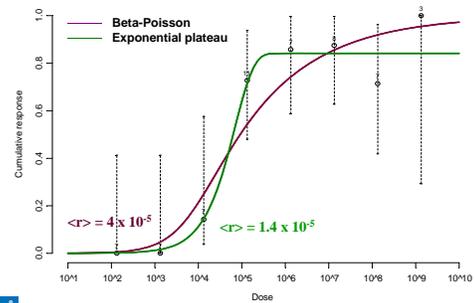
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## Modeling Infection

- Infection measures (sero-conversion, excretion)
- Fit dose-response models to data directly
- Compare fits statistically
- Select preferred model based on statistics and biological plausibility
- Data issues
  - Non-monotonicity
  - Lack of response “anchoring”

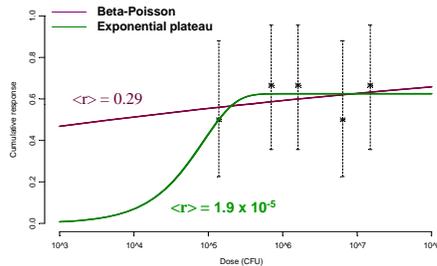
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## Rotavirus Infection Dose-Response



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## Salmonella derby Infection Dose-Response



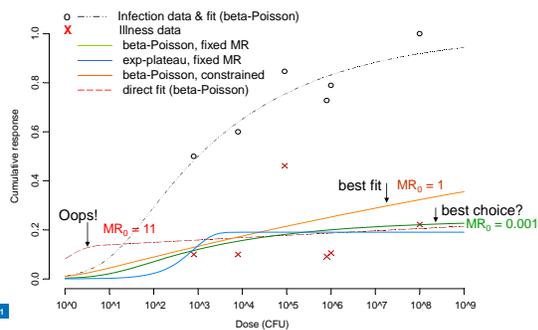
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## Modeling Illness

- Illness measures (GI symptoms)
- Fit models constrained on infection parameters
  - $Pr_{ILL} \leq Pr_{INF}$
- Pay attention to the morbidity ratio (MR)
  - Probability of illness given infection
  - Fixed or variable
  - $MR_0$  = morbidity ratio at unit dose
- Select preferred model based on statistics and biological plausibility

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## Campylobacter jejuni Illness Dose-Response



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## Human Population Variability

- Very little information
- *C. parvum* infectivity in sero-positive and sero-negative adult subjects
  - Sero-positive subjects much less susceptible
  - No data on sensitive subpopulations (go figure)
- Poliovirus administered to infants and adults
  - Infants less susceptible than adults (get out of town!)
  - Confounded by buffering issues
- *V. cholerae* administered with and without stomach-acid buffering
  - Unit infectivities might vary by orders of magnitude
  - Confounded by “response-anchoring” issues

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## Modeling Sensitive Subpopulations

- Simulation
  - speculative
- Safety & adjustment factors
  - very tricky
  - some applications (*Listeria*, *Salmonella*)
- Use animal data
  - data generally lacking
- Use epidemiological data
  - Salmonella* outbreak data

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## Pathogen Variability: Use of Surrogates?

- Infectivity of pathogens in any given category varies widely (8 O.M. for bacteria)
- Pathogenicity of closely related species can vary dramatically (4 O.M. for *Salmonella*)
- Infectivity & virulence across strains can vary substantially
  - *C. parvum* isolates (50-fold variation)
  - *E. coli* 157 vs *E. coli* 221 (death vs. diarrhea)
- Virulence factors not well defined
- Identifying a pathogen surrogate is a challenge
  - still an open issue

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## Host Surrogates? Human vs. Animal

- Defense mechanisms can be similar
- Endpoints can differ
- Pathogenic strains can differ
- Susceptibilities can differ
- Population variabilities differ
- Identifying a host surrogate is a challenge
  - still an open issue

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## Surrogates: Using Animal Data

- Apply directly with adjustment factors
  - hard to establish uncertainty bounds
- Establish sensitive subpopulation relative risk
  - extrapolate the relative risk, not the absolute risk
- Establish new animal models
  - swine, primates
  
- Estimate variability in pathogen virulence

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## Future Directions

- Artificial neural networks
  - make sense out of the nonsense?
- New animal models
  - swine, primates ?
- Mechanistic modeling
  - physiologically based
    - Salmonellosis (Coleman and Marks, 2000)
    - Cryptosporidiosis (Teunis et al., 2002)
    - Anthrax (Diamond et al., 2008)
    - Anthrax (Gutting, 2008)
    - Smallpox (Weir et al., 2008)
  - utilize animal and *in vitro* data
  - fundamental knowledge still lacking

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