

Dose Response Assessment of Agents of Concern and Implications for Risk Assessment

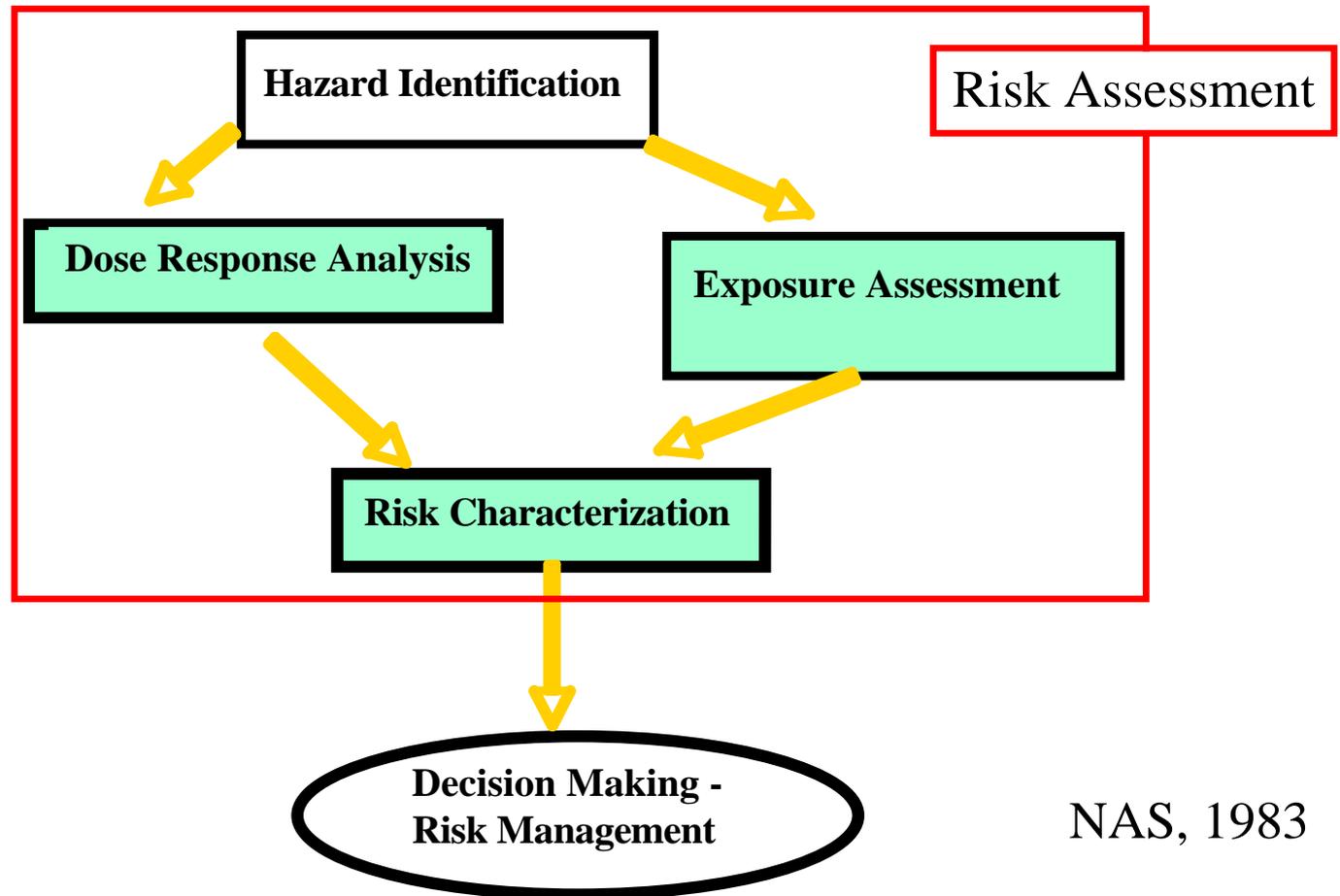


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Outline

- We have mined the open literature for useful data for agents of concern
- Summarize dose-response concepts and findings
- Significance to HS applications
- Open research needs/work in progress

DR Assessment & Risk Assessment



What is Dose-Response Assessment

- Development of mathematical relationship between dose and probability of response
- Enables low dose extrapolation

- Exponential

$$p = 1 - \exp(-kd)$$

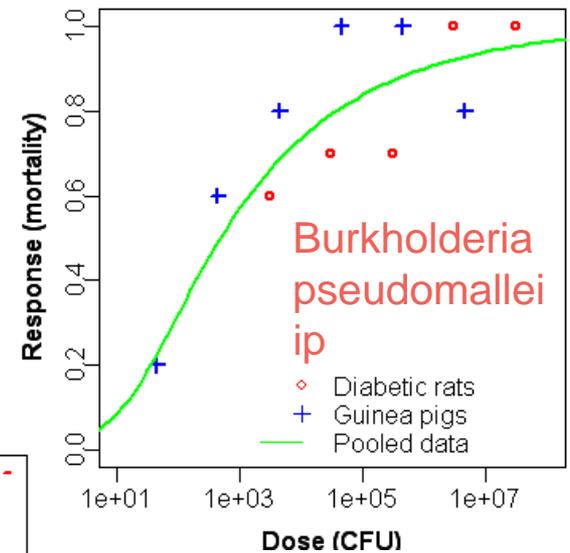
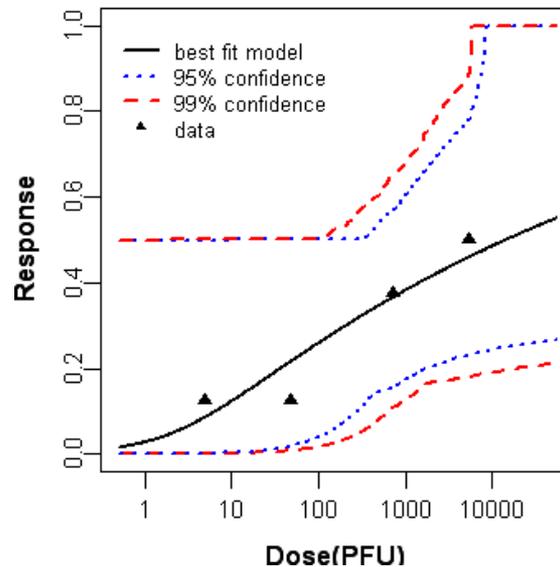
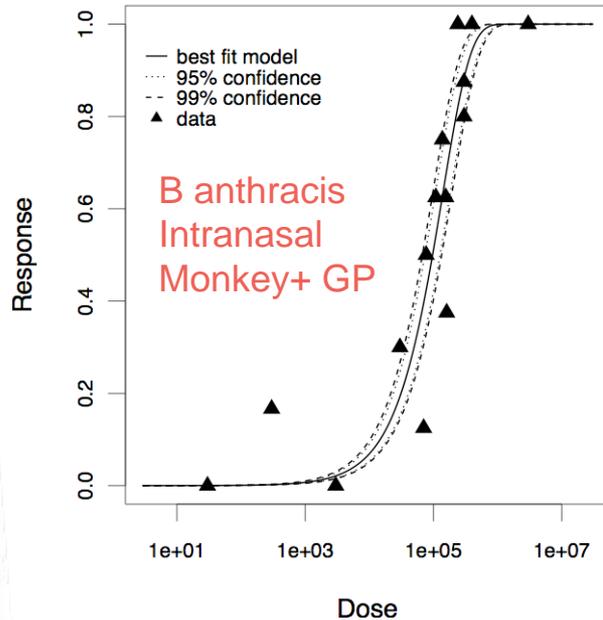
- Approximate Beta Poisson

$$p = 1 - \left[1 + \frac{d(2^{1/\alpha} - 1)}{N_{50}} \right]^{-\alpha}$$

Some Generalizations

- “Non threshold”/linear dose responses for infectious agents are applicable (based on ingested/inhaled doses)
- Animal->human extrapolation does not need interspecies factors if the animal host is competent
 - ◆ Based on prior work with non-bioterrorist agents

Example DR Curves



**Lassa Virus
inhalation, GP**

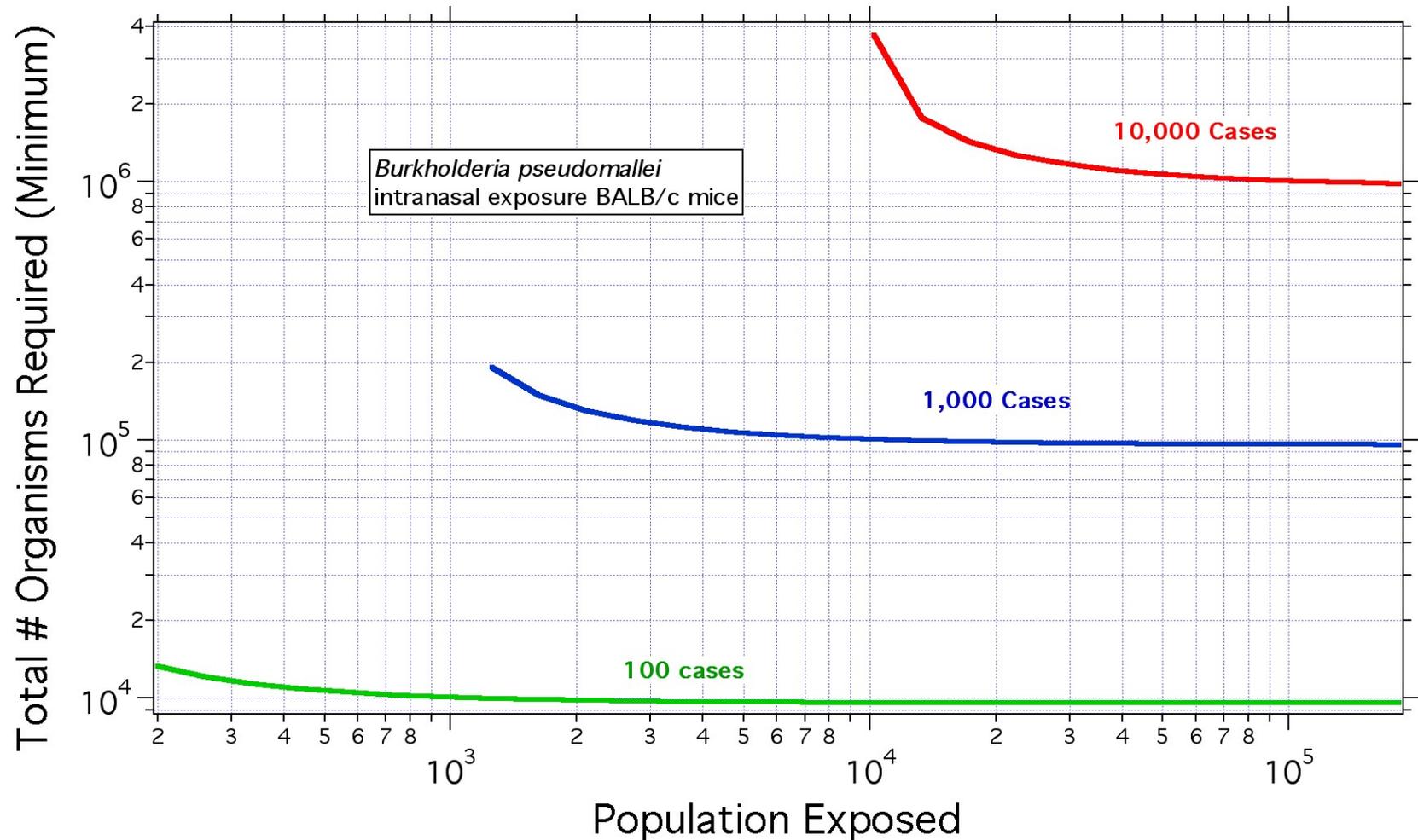
Catalog of “A” & “B” Agents Examined to Date

- ✓ Anthrax (*Bacillus anthracis*)
- ✓ Plague (*Yersinia pestis*)
- ✓ Smallpox (*variola major*)
- ✓ Tularemia (*Francisella tularensis*)
- ✓ Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])
- ✓ Food safety threats (e.g., *Salmonella* species, *Escherichia coli* O157:H7, *Shigella*)
- ✓ Glanders (*Burkholderia mallei*)
- ✓ Melioidosis (*Burkholderia pseudomallei*) • Psittacosis (*Chlamydia psittaci*)
- Q fever (*Coxiella burnetii*)
- Typhus (*Rickettsia prowazekii*)
- Viral encephalitis viruses
- ✓ Water safety threats

Incorporation of Other Factors

- Host age (smallpox)
- Time since dose (plague)
- Inhaled particle size (anthrax)

Relevance to Population Exposure



Relevance to Detection Systems

Estimated Dose for Single Exposure Risk of 1/100

Agent	Route	Animal	Dose
Smallpox	I.p.	mouse	1.79
B. anthracis	inhalation	monkey	1400
Lassa Virus	inhalation	outbred guinea pig	0.33
Plague	inhalation	monkey	125

Future Topics

- Physiologically Based Dose Response Models
- Route to Route Extrapolation
- Multiple Doses
- Role of Immunity
- Sensitive Subpopulations

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