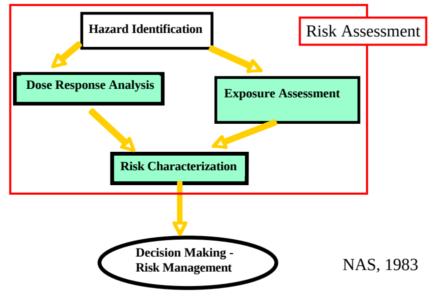
Dose Response Assessment of Agents of Concern and Implications for Risk Assessment

Charles N Haas
Drexel University
Co-Director, Center for Advancing Microbial Risk Assessment (CAMRA)

DR Assessment & Risk Assessment



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

What is Dose-Response Assessment

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

- Exponential

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

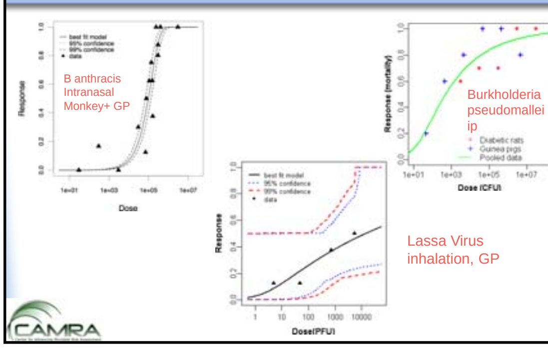
- Approximate Beta Poisson

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

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

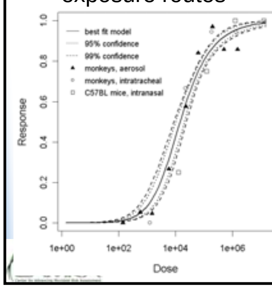
Example DR Curves

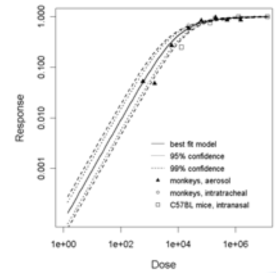


A few detailed examples

Inhalation Plague

- Integrating data from experiments with multiple exposure routes





Inhalation Plague

- Proposed Human Dose-Response Model
- Best fit provided by a beta-Poisson model with modified dose
- Best fit parameters

$$\alpha = 0.572$$

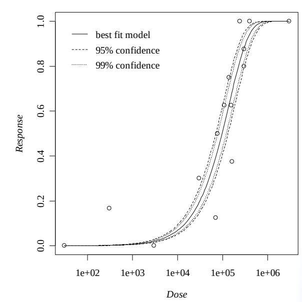
$$N_{50} = 112.7$$

$$s = 0.00774(\text{aerosol} \rightarrow \text{intratracheal})$$

	Dose	95% Confidence interval
LD_{50}	14,600	(10,630, 20,320)
LD_{10}	1255	(772.3, 2034)
LD_{1}	110.7	(68.1, 179.9)

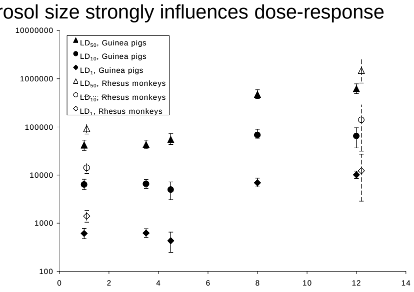
Inhalation Anthrax

- Refined dose-response model via pooling of data sets from two inhalation studies
- Data best fit by exponential model
  - $k = 7.15 \times 10^{-6}$
  - LD_{50} = 94,320
  - LD_{10} = 14,800



Inhalation Anthrax

- Aerosol size strongly influences dose-response

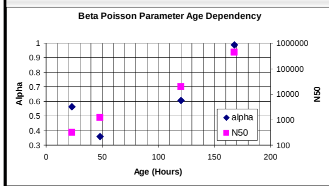


Smallpox Age Dependency

- Initial dose response assessment showed a good fit to the exponential and beta Poisson models. Log probit never showed a good fit to the data.

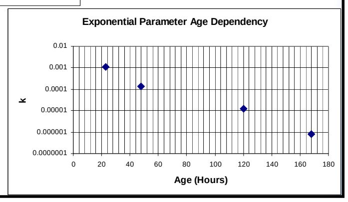
Age Group	Number of Doses	Model	Minimized Deviance	Degrees of Freedom	$\chi^2_{\alpha, n-k}$	P(fit)	Conclusion
0 to 24 hrs	5	Exponential	8.46	4	9.49	0.076	**Beta Poisson is best fitting model**
		Beta Poisson	**5.77**	**3**	**7.82**	**0.12**	
24 to 48 hrs	4	Exponential	18.67	3	7.82	0.0003	**Neither model is sufficient fit**
		Beta Poisson	8.81	2	5.99	0.012	
48 to 120 hrs	4	Exponential	6.60	3	7.82	0.086	**Beta Poisson is best fitting model**
		Beta Poisson	**1.09**	**2**	**5.99**	**0.58**	
120 to 168 hrs	4	Exponential	6.98	3	7.82	0.073	**Beta Poisson is best fitting model**
		Beta Poisson	**2.68**	**2**	**5.99**	**0.26**	

Smallpox Age Dependency



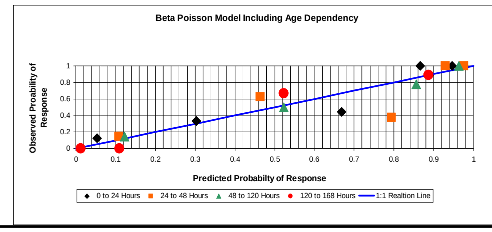
- Apparent trends appeared for both α and N_{50}.

- An apparent trend also appeared for k.



Smallpox Age Dependency

Group	Number of Doses	Model	Minimized Deviance	Δ	Difference in Degrees of Freedom	$\chi^2_{\alpha,1}$	Conclusion
Age Dependency	18	Exponential	262.77	22.27	1	3.84	Including age dependency allows better fit
No Age Dependency	18	Exponential	285.05		1		
Age Dependency	18	Beta Poisson	19.26	50.70	1	3.84	Including age dependency allows better fit
No Age Dependency	18	Beta Poisson	69.96		1		

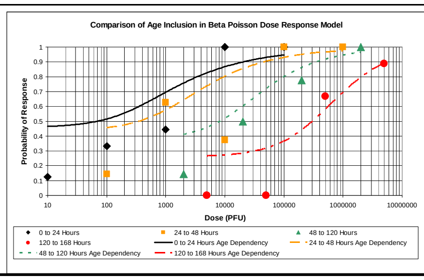


Smallpox Age Dependency

$$\alpha^* = \alpha_0 + \alpha_1 \cdot age$$

$$N_{50}^{\ *} = N_{50_0} \cdot e^{N_{50_1} \cdot age}$$

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



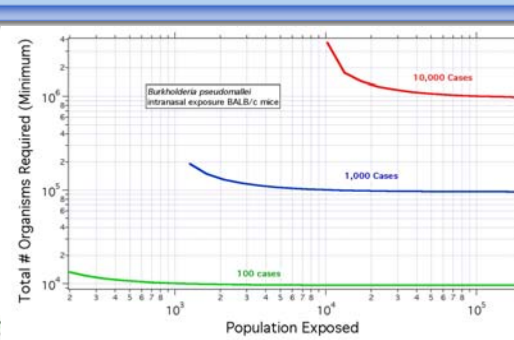
Catalog of "A" & "B" Agents Examined to Date

- ✓ 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

- Time since dose (plague)
- Host heterogeneity (Lassa)
- Health status (*Burkholderia*)

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

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Future Topics

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

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