

US EPA ARCHIVE DOCUMENT

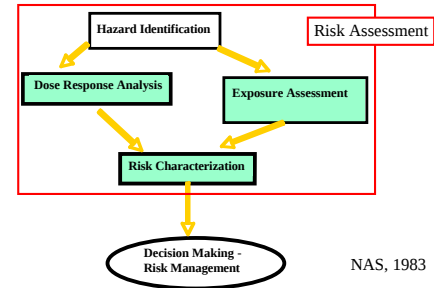
Dose Response Assessment of Agents of Concern and Implications for Risk Assessment



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DR Assessment & Risk Assessment



NAS, 1983



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
- Exponential
$$p = 1 - \exp(-kd)$$
- Enables low dose extrapolation
- Approximate Beta Poisson
$$p = 1 - \left[1 + \frac{d(2^{1/\alpha} - 1)}{N_{50}} \right]^{-\alpha}$$

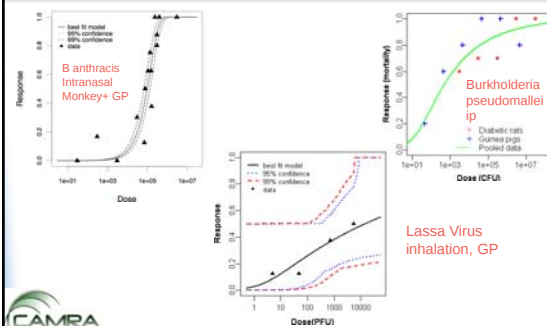


Some Generalizations

- “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

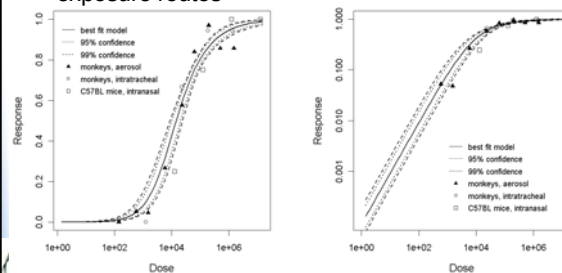


A few detailed examples



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

$$\alpha = 0.572$$

$$N_{50} = 112.7$$

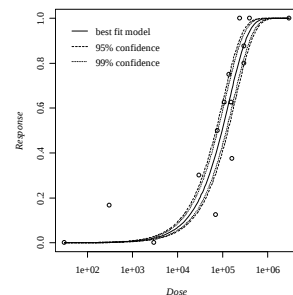
$$s = 0.00774(\text{aerosol} \rightarrow \text{intratracheal})$$

	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)



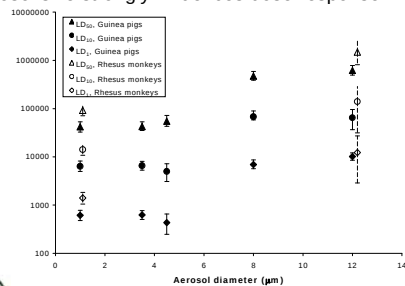
Inhalation Anthrax

- 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

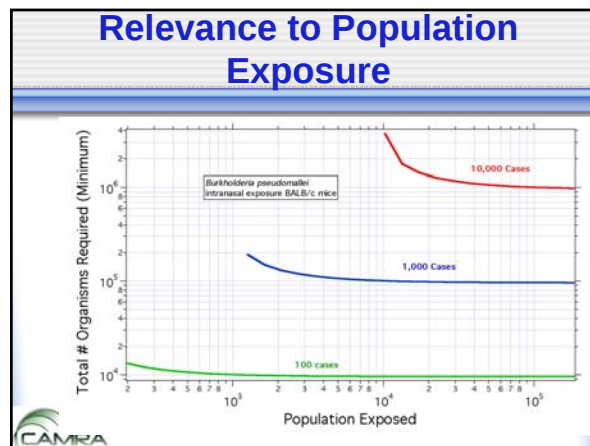
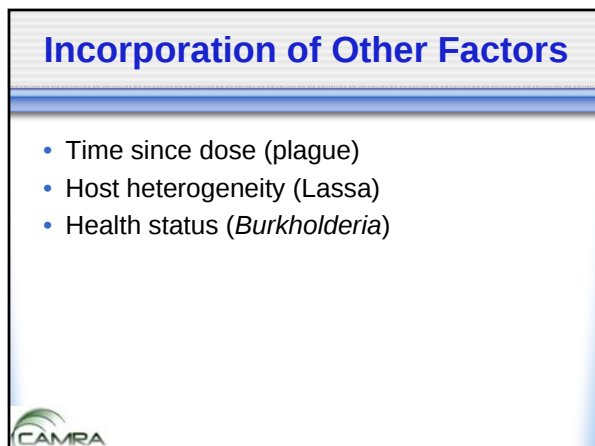
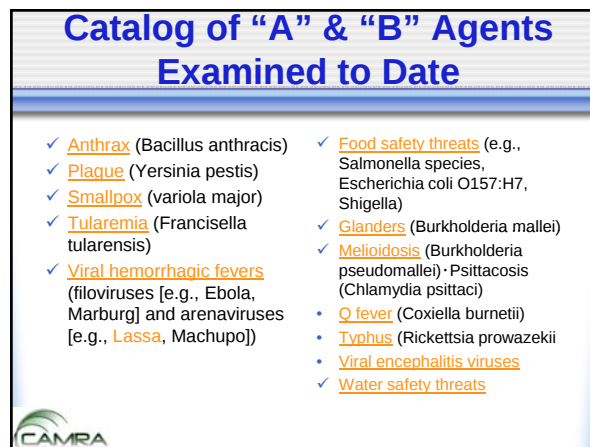
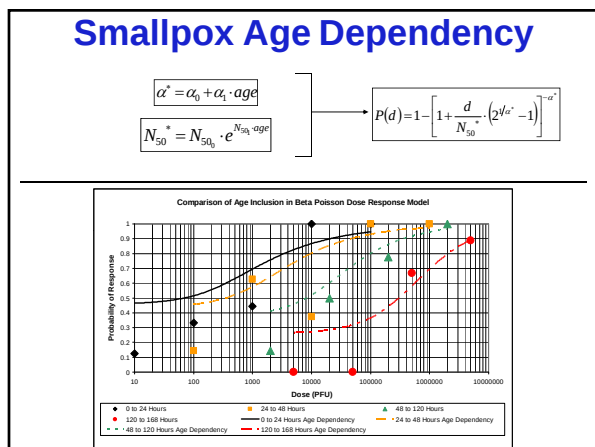
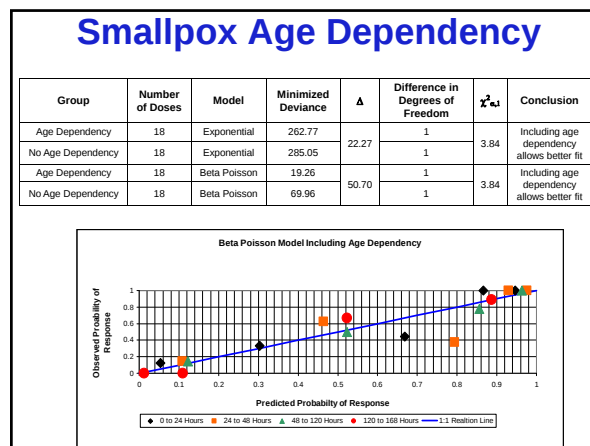
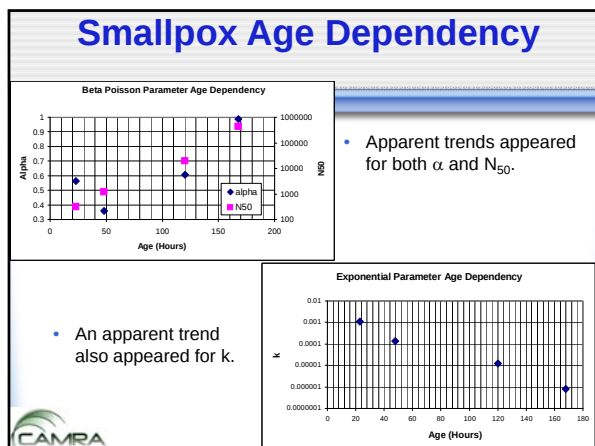


Smallpox Age Dependency

- 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	





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



Acknowledgments

- Funding Agencies
 - ♦ US EPA/DHS
 - ♦ Numerous other past sources
- CAMRA colleagues
 - ♦ Joan Rose
 - ♦ Chuck Gerba
 - ♦ Jim Koopman
 - ♦ Carole Bolin
 - ♦ Patrick Gurian
- Current students & researchers
 - ♦ Tim Bartrand
 - ♦ Mark Weir
 - ♦ Sushil Tamrakar
 - ♦ Yin Huang

