Uncertainty Modeling in Dose Response

Test data

7-18-07

The goal is to implement and compare different methods for quantifying the *uncertainty* in the probability of response, as a function of dose. Ultimately and ideally, this would be in a form compatible with integrated uncertainty analysis, comprising release, exposure, response, treatment cost, etc.

There have been delays in securing representative data sets. The ambitions in this exercise have been scaled back accordingly. The data sets 2-4 are real and are proposed by EPA as representative and relevant - so relevant that their names must be suppressed. Each has a simple "uncertainty issue" . Difficult extrapolations (subchronic-chronic, animal - human, precursor - endpoint) are avoided. Their analysis is hopefully rather straightforward. The goal is to get the different methods on the table.

1. BMD Tech guidance data

The first data set is from the BMD Technical Guidance document, it is chosen because it is simple and serves as demo for the BMD software.

\http://www.epa.gov/ncea/pdfs/bmds/BMD-External_10_13_2000.pdf

Dose	Number of Subjects	Number of Responses
0	50	1
21	49	15
60	45	20

2. Frambozadrine (combine males and females?)

	Dose(mg/kg-day)	Total no rats	Hyperkeratosis
Male			
	0	47	2
	1.2	45	6
	15	44	4
	82	47	24
Female			
	0	48	3
	1.8	49	5
	21	47	3
	109	48	33

Do we need separate DR relations for males and females?
Does combination alter the uncertainty in response?

3. Nectorine (Combine endpoints?)

	concentration (ppm)			
	0	10	30	60
Lesion	# response / # in trial			
Respiratory epithelial adenoma in rats	0/49	6/49	8/48	15/48
Olfactory epithelial neuroblastoma in rats	0/49	0/49	4/48	3/48

The summation of risks from multiple tumor sites when tumor formation occurs independently in different organs or cell types is considered superior to the calculation of risk from individual tumor sites alone.

The rats in each study were different, and only the indicated endpoint was sought in each study. What is the uncertainty in response as function of dose for either respiratory epithelial adenoma OR olfactory epithelial neuroblastoma in rats

4. Persimonate (Combine studies?)

	continuous equivalent	total metabolism (mg/kg-day)	survival adjusted tumor incidence
B6C3F1 male mice inhalation	0	0	17/49
	18ppm	27	31/47
	36ppm	41	41/50
Crj:BDF1 male mice inhalation	0	0	13/46
	1.8ppm	3.4	21/49
	9.0ppm	14	19/48
	45 ppm	36	40/49

Can we combine these studies? Does it affect our uncertainty?