Statistical Analysis of Tumor Data from Carcinogenicity Studies

Regulatory agencies and research institutes agree that, in the statistical analysis of tumor data from a 2-year carcinogenicity study, it is essential to adjust for differences in intercurrent mortality among treatment groups regardless of how small those differences may be. Two methods are outlined in the 2001 FDA CDER draft Guidance (1).

Peto: The Peto approach takes into account the context in which tumors were observed as determined by a pathologist. Tumors not directly responsible for an animal's death are classified as incidental. Tumors directly responsible for an animal's death are classified as fatal. Tumors that can be detected in-life are classified as mortality-independent. Peto methodology combines the prevalence, death-rate, or onset-rate method depending on whether the tumor was observed in incidental, fatal, or mortality-independent context.

Poly-k: The poly-k approach does not require the context of observation information. Rather, the methodology adjusts the number of animals at risk per treatment group to reflect intercurrent mortality. The basis of this adjustment is that tumor onset rates often increase with age according to an approximate power-law relationship. This adjusted denominator is then used in a modified Cochran Armitage test.

Discussion: Both tests are statistically robust provided that the mortality rates from non-tumor causes are similar among treated groups. However, the Peto test becomes less robust with deviations from that assumption. In addition, the Peto test is fully dependent on cause of death information and therefore cannot be conducted if the information is not captured or not reliable.

The poly-k test does not take into account whether or not the tumor contributed to the animal's death and does not take into account the time to tumor detection. An animal that presents a tumor in week 50 is treated the same as an animal that presents a tumor at the scheduled week 104 necropsy. And an animal that dies at week 80 with a tumor is weighted more heavily in the analysis than one that dies at week 80 without the tumor even though both animals were at risk for the same amount of time.

Regulatory Perspective: The 2001 FDA CDER draft Guidance suggested that Peto testing should be conducted when cause of death information is available and poly-k testing conducted when it is not available or not reliable. Literature reviews (2,3) indicate that, since the draft guidance, FDA statisticians have begun conducting both poly-k and Peto analysis in their reviews of carcinogenicity studies. NTP studies are being analyzed using poly-k. Most European submissions include the Peto analysis in order to be consistent with FDA guidance but also conduct and prefer the Poly-k analysis.

BioSTAT Perspective: Until the draft guidance is updated, there is a place for both the Peto and poly-k analysis in the statistical review of tumor data for 2-year carcinogenicity studies. Statistical analysis results in the form of p-values are simply one tool to aid in the overall interpretation of the carcinogenicity study. The analysis results should be used in conjunction with the weight of evidence from other sources such as non-neoplastic findings, historical control data, and other studies with the same test article to draw conclusions.

Expanded Decision Rules (4)

	Significance Levels: R=Rare tumor C=Common Tumor		
	1-sided Trend Test alone	**Control-High Comparison alone**	**Trend and Control-High jointly**

Standard 2-year studies with two species and two sexes	C: 0.005 R: 0.025	C: 0.01 R: 0.05	Trend
			   C: 0.005 R: 0.025
			
			Control-High
			   C: 0.05 R: 0.10

Alternative ICH studies (one 2-year study and one short/mid-term alternative study)	2-year study
	  C:0.005 R:0.025
	
	Alternative study
	  C:0.05 R:0.05
		2-year study
		  C:0.01 R:0.05
		
		Alternative study
		  C:0.05 R:0.05
			2-year study Trend
			  C: 0.005 R: 0.025
			
			2-year study Control-High
			  C: 0.05 R: 0.10
			
			Alternative Study
			Trend and Control-High
			  C: 0.05 R: 0.10

Standard 2-year study with one species only and two sexes	C: 0.01 R: 0.05	C: 0.025 R: 0.10	Trend
			   C: 0.01 R: 0.05
			Control-High
			   C: 0.05 R: 0.10

References:

1) *Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals*; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, May 2001 (Draft).

2) Kodell, RL (2012): *Should We Assess Tumorigenicity With the Peto or Poly-k Test?*, Statistics in Biopharmaceutical Research, 4:2, 118-124.

3) Rahman, M.A., Shen, M., Dong, X., Lin, K.K., & Tsong, Y. (2016). Regulatory Nonclinical Statistics. In L. Zhang (Ed.), *Nonclinical Statistics for Pharmaceutical and Biotechnology Industries* (pp. 19-31). Springer International Publishing Switzerland

4) Lin, K.K. & Rahman, M.A. (2018). Expanded Statistical Decision Rules for Interpretations of Results of Rodent Carcinogenicity Studies of Pharmaceuticals. In K.E. Peace et al. (Eds.), *Biopharmaceutical Applied Statistics Symposium* (pp. 151-181). Springer Nature Singapore Pte Ltd.

Additional Reading:
Statistical Methods for Carcinogenicity Studies, Toxicologic Pathology, vol 30, no 3, pp 403–414, 2002.

Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 AND 453, 2nd edition; OECD Environment, Health and Safety Publications, Series on Testing and Assessment.